Hans-Georg Dederer
Gregor Frenken *Editors*

Regulation of Genome Editing in Human iPS Cells

A Comparative Legal Analysis of National Regulatory Frameworks for iPSC-based Cell/Gene Therapies

Springer

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ISBN 978-3-030-93022-6 ISBN 978-3-030-93023-3 (eBook)
https://doi.org/10.1007/978-3-030-93023-3

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Preface

This volume forms, predominantly, a collection of country reports on the regulation of genome editing in human induced pluripotent stem cells (iPSCs). The country rapporteurs are from France, Germany, Japan, Korea, Switzerland, and the United States. The regulatory framework of the European Union (EU) is captured by the reports on France and Germany. The focus of the country reports is on somatic cell/gene therapies based on genome-edited iPSCs. However, the reports also throw a glance at the regulation of germ line therapies. In addition, a special section of the reports is devoted to the protection of the patients' biological data.

The country reports are preceded by a chapter which provides an introduction into the scientific foundations of iPSC technology and the treatment of hereditary diseases through the use of genome-edited iPSCs. The last chapter following the country reports includes a comparative analysis, the purpose of which is to identify best regulatory practices in the field of genome-edited iPSC-based cell/gene therapies.

The country rapporteurs presented their draft reports on the occasion of a workshop titled "Genome Editing in Human iPS Cells: A Comparative Analysis of Regulatory Frameworks of Selected Countries and the EU" which was held in Munich (Germany) on 19–20 September 2019. The stimulating discussions are reflected in the final versions of the country reports as published in this volume. Although the country reports are based on the talks given at the Munich workshop, the country rapporteurs took into account, as the case may be, later developments as well.

The workshop was part of an interdisciplinary research project, the title of which was "Revisited ethical and legal concepts for precise genome engineering approaches of hereditary diseases," its acronym being "REALiGN-HD." The scientifically informed ethical-legal project was funded by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung—BMBF; reference no. 01GP1616) for the period from October 1, 2016 to December 31, 2020. The three research groups of the consortium were located at the Hannover

Medical School (medicine/developmental biology), the Philosophical-Theological University of Vallendar (ethics), and the University of Passau (law).

The venue of the workshop were the wonderful premises of the Carl Friedrich von Siemens Stiftung which form part of the magnificent Nymphenburg Palace situated in the city center of Munich. The foundation also provided the excellent catering throughout the two-day workshop.

The organization of such a workshop and the publication of a multi-author volume are endeavors, the success of which depends on numerous people who unwaveringly pursue a common goal through constant fruitful collaboration. Therefore, sincere thanks are given, first of all, to the authors, i.e., in alphabetical order, Hans Peter Bernhard, Tobias Cantz, Aurélie Mahalatchimy, Akifumi Matsuyama, Hanayuki Okura, Kathleen M. Sanzo, Rainer J. Schweizer, Yu-Cheol Shin, and Antonia S. Straden. We would also like to thank the members of our research team at the University of Passau, i.e. Florian Alkofer, Ştefan Cravcişin, Luca Lüneburg, Hannah Lüttge, Stefan Rieger, Pia Storf, and Sophia Wagner, who contributed significantly to our internal debates and took care of all kinds of organizational matters. Furthermore, we would like to express our special gratitude toward our sponsors, i.e. the BMBF and, as regards the workshop, the Carl Friedrich von Siemens Stiftung, as well as toward the DLR Project Management Agency and the University of Passau both of which ensured the smooth and success-oriented administration of our project. Finally, we would like to thank our publishing house, i.e. Springer Nature, especially Brigitte Reschke, the executive editor, Abdus Salam Mazumder, the project coordinator, and Jana Yagnavaragan, the project manager, for continually excellent and trustful co-operation.

Passau, Germany
October 2021

Hans-Georg Dederer
Gregor Frenken

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About the Editors

Hans-Georg Dederer was born on January 24, 1967 in Stuttgart, Germany. After studying law in Tübingen and Konstanz (1988–1992), he completed his legal clerkship with stations in Konstanz and Washington, D.C. (1992–1995) before pursuing his doctoral studies (Dr. iur., 1997), followed by the *venia legendi* (Habilitation, 2003), at the University of Bonn. Between 2003 and 2008, he was an Associate Professor in Bonn and a visiting professor at the Universities of Bonn, Düsseldorf, Tübingen, and Passau. Since 2009, he holds the Chair of Constitutional and Administrative Law, Public International Law, European and International Economic Law at the University of Passau. Hans-Georg Dederer's list of publications also includes monographs, articles, and commentaries in the field of life sciences law. His expertise in the field has been called upon by federal ministries, federal and state parliaments as well as the National Academy of Sciences Leopoldina. Since 2018, Hans-Georg Dederer is also a member of the Permanent Senate Commission of the German Research Foundation (DFG) on Genetic Research.

Gregor Frenken was born on June 15, 1994 in Neustadt an der Aisch, Germany. Following the completion of his law degree as a grantee of the prestigious German Academic Scholarship Foundation in 2018, he joined the REALiGN-HD research group headed by Hans-Georg Dederer and funded by the Federal Ministry of Education and Research. Since 2020, he is a Graduate Research and a Teaching Assistant at the Chair of Hans-Georg Dederer.

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Chapter 1
Introductory Remarks

Hans-Georg Dederer

Abstract This introductory chapter will deliver insight into the background of this volume which forms an important outcome of an interdisciplinary research project. At the core of the project are two basic scenarios for the future treatment of hereditary diseases. The envisaged treatments may constitute either germ line therapies or somatic cell/gene therapies. Genome editing, especially by means of CRISPR/Cas, and induced pluripotent stem cells (iPSCs) form the essential scientific and technological components of these two therapeutic approaches. Research and development of such therapies are governed by various laws and regulations, though. Overly restrictive regulatory frameworks may slow down scientific and technological progress which is why governments may be tempted to downgrade domestic regulations in order to promote the translation of basic research into clinical applications. Hence, a certain degree of regulatory competition exists between States. Against this background, it is of particular interest how different countries regulate genome-edited iPSC-based somatic cell/gene therapies and germ line therapies. This first chapter will only summarily highlight some of the many notable aspects of the different national regulatory frameworks as portrayed by the respective country rapporteurs. It will also outline some of the prominent features of the second chapter (on the scientific foundations of iPSC and CRISPR/Cas technology) and the last chapter (*i.e.* the comparative analysis intended to consolidate insights gathered from the country reports).

1.1 Introduction

The reprogramming of human somatic cells into induced pluripotent stem cells (iPSCs) and the subsequent re-differentiation of iPSCs into therapeutically desired cells to be transplanted or injected into patients has universally been recognized as a powerful and even revolutionary tool of modern regenerative medicine. The same

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H.-G. Dederer, G. Frenken (eds.), *Regulation of Genome Editing in Human iPS Cells*, https://doi.org/10.1007/978-3-030-93023-3_1

holds true for the genetic modification of human cells through methods of so-called genome editing, especially by means of CRISPR/Cas.[1] This has been amply demonstrated by the award of Nobel Prizes: first, in 2012, to John B. Gurdon and Shinya Yamanaka[2] for their seminal research on the reprogramming of somatic cells and the generation of iPSCs in particular[3] and, second, in 2020, to Emmanuelle Charpentier and Jennifer A. Doudna[4] for their equally epoch-making research on CRISPR/Cas9.[5]

It stands to reason that a combination of both technologies, *i.e.* iPSC and CRISPR/Cas technology, may produce unprecedented progress in both basic and translational research aiming at innovative treatments of hereditary diseases, especially of diseases which are severe and hitherto incurable. It is likewise obvious that the novelty and complexity of related clinical research and resultant therapies raise intricate and intriguing ethical and legal challenges which call for an intense interdisciplinary analysis.

1.2 Background to This Volume

1.2.1 The REALiGN-HD Research Consortium

Thus, rather unsurprisingly, back in 2015, the German Federal Ministry of Education and Research (BMBF)[6] issued a call for applications regarding the funding of projects on ethical and legal implications of genome editing. This call prompted researchers from the Philosophical-Theological University of Vallendar (PTHV),[7] the Hannover Medical School (MHH)[8] and the University of Passau (UP)[9] to form a research consortium[10] which, finally, succeeded in receiving a grant enabling the research teams to carry out ethical and legal research on the basis of latest biological and medical insights into human genome editing and iPSC technology.

[1] CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; Cas: CRISPR-associated. Regarding CRISPR/Cas and iPSCs see Cantz (Chap. 2), *sub* 2.1 and 2.4.

[2] Nobel Prize in Physiology and Medicine.

[3] The key publications being: Gurdon (1962); Takahashi and Yamanaka (2006).

[4] Nobel Prize in Chemistry.

[5] The key publication being: Jinek et al. (2012).

[6] Bundesministerium für Bildung und Forschung.

[7] Philosophisch-Theologische Hochschule Vallendar.

[8] Medizinische Hochschule Hannover.

[9] Universität Passau.

[10] With the principal investigators (PIs) being: Professor Dr. Dr. Thomas Heinemann (ethics; PTHV), Professor Dr. Tobias Cantz (medicine, developmental biology; MHH), and Professor Dr. Hans-Georg Dederer (law; UP).

The acronym of the research project was 'REALiGN-HD' representing the full title of the project which was: 'Revisited ethical and legal concepts for precise genome engineering approaches of hereditary diseases'. Hence, the research consortium chose to focus on genome editing, in particular of iPSCs, as novel tools to cure hereditary diseases of human beings.

1.2.2 Treatment of Hereditary Diseases: Two Scenarios

The basic idea of the project was that human hereditary diseases may be treated in two ways both of which pose peculiar ethical and legal problems.

First, one way of treatment could be genome editing of the human embryo at the zygote stage (*i.e.* at the single-cell-embryo stage) or, even earlier, at the pronucleus stage. Another route might be to genetically alter iPSC-derived gametes (*i.e.* egg or sperm cells)[11] before *in vitro* fertilization. As a result of such treatments, the germ line of the resultant human being is genetically modified which implies that the genetic correction is transmitted to his or her descendants. Accordingly, these kinds of treatment are germ line therapies (scenario 1).

Second, another way of treatment could be genome editing of patient-specific iPSCs which are differentiated into somatic cells to be re-transplanted or injected into the patient.[12] This constitutes, in the end, an autologous cell therapy combined with a somatic *ex vivo* gene therapy, *i.e.*, in short, a somatic cell/gene therapy (scenario 2).

A practical example could be the treatment of cystic fibrosis which is a severe and hitherto uncurable hereditary disease affecting, in particular, the lungs of the patient. What needs to be corrected is a mutation of the CFTR gene.

Accordingly, on the one hand (scenario 1), cystic fibrosis could be treated through genome editing of the human embryo at the zygote stage, or at the pronuclear stage, or of, *e.g.*, iPSC-derived gametes before *in vitro* fertilization. This results in a genetic modification of the germ line and, therefore, affects the embryo's offspring and, thus, future generations as well.[13]

On the other hand (scenario 2), cystic fibrosis could be treated by genome editing of patient-specific iPSCs as well. This autologous therapy would include the following steps: (1) biopsied somatic cells of the patient are reprogrammed into iPSCs *in vitro*, (2) these iPSCs are genetically corrected using, *e.g.*, CRISPR/Cas, (3) the corrected genome-edited iPSCs are differentiated, *e.g.*, into the desired pulmonary cells, (4) these cells are re-transplanted into the patient's lungs which will, hopefully, replace the cells affected by cystic fibrosis.

[11] On iPSC-derived germ cells see Cantz (Chap. 2), *sub* 2.3.

[12] Regarding this therapeutic approach see Cantz (Chap. 2), *sub* 2.2 and 2.4.

[13] This scenario is further fleshed out by Cantz (Chap. 2), *sub* 2.5, also proposing the concept of a 'one-generation germ line therapy'.

1.2.3 Regulatory Competition Between States

Against the background of these therapeutic scenarios, one of the aims of REALiGN-HD was to gain insights into foreign regulatory frameworks applicable to such therapies which are, ultimately, either germ line therapies (scenario 1) or somatic cell/gene therapies (scenario 2) respectively (*supra sub* 1.2.2). For this purpose, experts prepared reports on the applicable regulatory framework of countries which are leading in the field of both iPSC technology and genome editing. Among these countries are, in alphabetical order, France, Germany, Japan, Korea, Switzerland and the United States. The country reports form the Chaps. 3–8 of this volume.

But why do foreign regulatory frameworks matter at all? First, studying regulatory frameworks of other States broadens our knowledge of how such innovative therapies might be regulated. More importantly, second, such knowledge enables us to identify potential strengths and weaknesses of our own regulatory framework. This, in turn, enables us, third, to make well-founded recommendations to our own legislators or regulators if we consider our laws and regulations to be inappropriate or incomplete.

However, there is still one more point which is, fourth, regulatory competition between national economies. Indeed, laws and regulations may exert a decisive influence on the competitiveness of universities, or research institutions respectively, and pharmaceutical industries regarding research and development of innovative medicinal products. On the one hand, strict regulation is required to ensure safety, efficacy and quality of novel therapeutic products. However, the stricter the regulation the more burdensome, the lengthier and the costlier are research, development and market entry of new drugs and therapies. Therefore, researchers and developers of novel medicinal products in countries with very strict regulation may face a competitive disadvantage as compared to their competitors in other jurisdictions who enjoy a more permissive regulatory landscape.[14] Accordingly, governments may consider deregulation a promising tool to foster competitiveness.

In fact, an article published in August 2019 reflected on the problem of the "Downgrading of regulation in regenerative medicine".[15] The authors point to certain developments first in Korea, then in Japan, concerning deregulation in the field of stem cell-based medicinal products.[16] Since then, the authors continue, regulatory frameworks in other countries, including the United States, have come under pressure.[17]

[14] In this regard, *cf.* also the "global 'snapshot' of the spectrum of policy and legislative approaches (restrictive to permissive)" with a view to, *inter alia*, germ line therapy and somatic gene therapy, by Isasi et al. (2016).

[15] Sipp and Sleeboom-Faulkner (2019).

[16] Sipp and Sleeboom-Faulkner (2019), p. 645.

[17] Sipp and Sleeboom-Faulkner (2019), p. 646.

1.2.4 Anticipating the (Near) Future

Of course, the highly innovative therapies envisaged by the REALiGN-HD consortium[18] are, for the time being, still fiction. However, research on regenerative medicine advances and evolves at an unprecedented pace producing unimaginable results. Japan, *e.g.*, has already authorised clinical trials concerning iPSC-based therapies of hitherto incurable severe diseases: macular degeneration, Parkinson's Disease and spinal cord injuries.[19] Apparently, the iPSCs used for these clinical studies have not been genetically modified through genome editing, though.

Nevertheless, regenerative medicine on the basis of genome-edited cells, including genome-edited iPSCs, may be just ahead of us. CRISPR/Cas seems to have become the preferred tool for genetic modifications in plants, animals and humans. Its precision, efficacy, cost-efficiency, and simplicity are unsurpassed. Indeed, it seems not to be too far-fetched to consider CRISPR/Cas a technique that transforms modern biotechnology into a disruptive technology, just like artificial intelligence, nanotechnology and synthetic biology. The combined application of these technologies on human beings might lead to transformations of individual human life and of our societies which could shock the constitutive basis of our moral and legal norms and values as they have developed over the last five hundred years, *i.e.* beginning with Renaissance, until today. Will, especially, regenerative medicine based on iPSC and CRISPR/Cas technology realize an age-old dream: the fountain of youth?[20] Is immortality the future of humankind?[21]

The future of human genome editing has already closed in on us. In November 2018, He Jiankui, a young Chinese researcher, claimed to have modified the germ line of twin girls using the CRISPR/Cas technique. He announced the birth of the two genome-edited babies on the occasion of the Second International Summit on Human Genome Editing in Hongkong.[22] The purpose of the germ line intervention was to immunize the children against HIV infection through a knock-out of the CCR5 gene. He's revelation generated a global storm of protest, especially among scientists of highest reputation, but also sparked a worldwide debate on whether germ line interventions are acceptable at all, and, if so, under what conditions.[23] The current consensus within the scientific community seems to be that scientists should adhere to a self-imposed moratorium on any clinical germ line interventions.[24] If the

[18] See *supra sub* 1.2.2.

[19] See, *e.g.*, Cyranoski (2019).

[20] *Cf.*, *e.g.*, the famous painting 'Der Jungbrunnen' of 1546 by Lucas Cranach der Ältere (1472–1553) (available at: https://en.wikipedia.org/wiki/The_Fountain_of_Youth_(Cranach)).

[21] See, *e.g.*, Gabbatt (2019).

[22] See, *e.g.*, Cyranoski and Ledford (2018).

[23] An impressive outcome of these international debates is the recently released report by the National Academy of Sciences (2020). See also the joint statement by the Comité Consultatif National d'Éthique pour les sciences de la vie et de la santé et al. (2020).

[24] See, *e.g.*, Lander et al. (2019).

human germ line was to be universally considered heritage of humankind,[25] we should expect that the international community of states agree on legally binding or, at least, 'soft law' rules regarding germ line interventions and that such rules should apply in any part of the world in the same way.[26]

As regards somatic cell/gene therapies, a most recent publication reported the successful infusion of autologous hematopoietic stem and precursor cells which had been genetically modified by means of CRISPR/Cas9 in order to produce fetal haemoglobin.[27] The two patients receiving this somatic cell/gene therapy treatment suffered from transfusion-dependent β-thalassemia (TDT) and sickle cell disease (SCD) respectively. This clinical study was hailed as "the first published account of using the gene-editing system [CRISPR/Cas9] to treat heritable diseases" providing "an important proof of concept for that technology".[28]

Hence, it seems to be only a matter of time, until we see the first ever clinical study, or clinical trial respectively, with genome-edited iPSC-based somatic cell/gene therapy products. Regarding the regulation of such therapies, or medicinal products respectively, one should expect more or less similar regulations in all jurisdictions since the science and technology underlying these therapies, *i.e.*, in our case, iPSC technology and genome editing through CRISPR/Cas, are the same everywhere. Nevertheless, national regulatory frameworks might differ markedly. One of the reasons for such differences has already been mentioned (*supra sub* 1.2.3): regulatory competition between national economies. Other reasons for downgrading laws and regulations in order to enhance research, development and market entry of innovative therapeutic products might be not of a purely economic, but rather of a social nature. *E.g.*, aging societies of developed states (such as the German and Japanese societies) may consider regenerative medicine a most promising approach to cure diseases which result from age-related degeneration of cells, tissues and organs. Of course, the strictness or permissiveness of laws and regulations also depend on a country's history, its culture and prevailing public morals. That holds true, in particular, in the field of regenerative medicine and, more generally, in the field of biomedicine.

[25] *Cf.* Article 1 of the UNESCO Universal Declaration on the Human Genome and Human Rights of 11 November 1997 according to which "[t]he human genome . . . [i]n a symbolic sense . . . is the heritage of humanity".

[26] See the efforts of the World Health Organization (WHO) which established a 'WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing'.

[27] Frangoul et al. (2020).

[28] Ledford (2020a). See, however, also Ledford (2020b), reporting that "[a] person has become the first to receive a CRISPR-Cas9 gene therapy administered directly into their body" aiming at the treatment of Leber's congenital amaurosis 10 (LCA10). The difference is that the latter therapy (concerning LCA10) is an *in vivo* gene therapy whereas the former (concerning TDT and SCD) is an *ex vivo* gene therapy.

1.3 Overview of the Volume

The country reports in this volume will provide illuminative insights into the regulatory approaches of the respective States as regards somatic cell/gene therapies based on genome-edited iPSCs. This section is intended to provide a brief sketch of the country reports (Chaps. 3–8) and the chapters framing them (Chaps. 2 and 9). Of course, the authors speak for themselves. Hence, we will highlight only some particular aspects of those chapters. Especially, as regards the country reports, the overview will try to focus on those features which, form the subjective point of view of this chapter's author, genuinely distinguish the respective regulatory framework.

1.3.1 Scientific Foundations

Chapter 2 by Tobias Cantz provides an insightful introduction to, *inter alia*, iPSC technology and genome editing. As regards genome edited iPSC-based therapies, Tobias Cantz underlines the importance of "most rigid quality controls and safety analyses". Apparently, reprogramming of somatic cells into iPSCs and re-differentiation of iPSCs into therapeutically desired cells may cause "chromosomal abnormalities". This problem might be even exacerbated if the iPSCs are genetically engineered in order to correct the genetic defect which is at the origin of the particular hereditary disease. In order to detect any genomic aberrations, full sequencing at least of the genome, but also, as the case may be, of the transcriptome and the proteome, is inevitable. This, in turn, means that the entire spectrum of the donor's or the patient's genetic, transcriptomic and proteomic data is disclosed raising ethical and legal issues of personal data protection. On the other hand, genetic correction of iPSCs seems to be a preferred way of somatic cell/gene therapies since the genetically modified iPSCs, or the cells derived therefrom, form "(clonally) expandable cells, from which an aliquot can be used for detailed genetic analyses" ensuring, thus, the safety, efficacy and quality of the final cell/gene therapy products to be administered to the patient. Tobias Cantz also assesses the possibilities of a germ line therapy approach using cystic fibrosis as an example of a severe and hitherto incurable hereditary disease. In particular, he suggests a most striking concept, *i.e.*, a 'one-generation germ line therapy'. The purpose of such an approach is to allow for a germ line therapy, if specifically needed (as in the case of a couple with both partners suffering from cystic fibrosis),[29] which leaves the germ line of the descendants unaltered. Consequently, *e.g.*, unknown and unpredictable adverse long-term effects resulting from germ line editing, but manifesting only in future generations are ruled out. In addition, also the integrity of the natural germ line of the human species as such is preserved.

[29] Since in such a situation, even preimplantation genetic diagnosis (PGD) could not prevent that any off-spring would suffer from cystic fibrosis.

1.3.2 EU Member States: France and Germany

The country reports on Germany by Gregor Frenken and Hannah Lüttge (Chap. 3) and on France by Aurélie Mahalatchimy (Chap. 4) provide an impressive picture of the complexities of a multi-layered regulatory framework made up of domestic and European Union (EU) law. Both authors classify genetically corrected cells derived from genome-edited iPSCs as 'gene therapy medicinal products' and, as a result, as 'advanced therapy medicinal products' (ATMPs) within the meaning of EU medicinal products law. Placing on the market of ATMPs requires, as a rule, prior marketing authorization by the European Commission. By way of exception, an ATMP not, or not yet, authorized by the European Commission may be made available to individual patients or patient groups on the basis of domestic law, albeit solely under certain restrictions originating in EU law. These restrictive requirements are laid down in certain provisions known as the 'hospital exemption', the 'special needs exemption' and the 'compassionate use exemption'. While the 'special needs exemption' and the 'compassionate use exemption' are options only, *i.e.* EU Member States may freely decide whether they want to implement them or not, the 'hospital exemption' has to be implemented into domestic medicinal products law. *E.g.*, contrary to France, Germany chose not to make use of the 'special needs exemption'. On the other hand, both countries have adopted the 'hospital exemption'. However, the French 'hospital exemption' seems to be more narrowly-tailored than its German counterpart. This confirms the general perception that the EU Member States have implemented the 'hospital exemption' quite differently. Even worse is the regulatory fragmentation on the Member State level as regards GMO law, *i.e.* the rules governing genetically modified organisms (GMOs). GMO law may come into play, *e.g.*, in cases of clinical trials. In light of a judgment of 2018 by the Court of Justice of the EU (CJEU), genome-edited cells have to be considered GMOs within the meaning of the pertinent EU directives. Accordingly, regarding clinical trials of genome-edited iPSC-based cell/gene therapies, EU law on GMOs is applicable in general and, thus, domestic law implementing the relevant EU directives as well. The regulatory jumble resulting from the divergent implementation and enforcement of these GMO-related EU directives can be illustrated by the differing regulatory approaches of France, on the one hand, and Germany, on the other hand. Regarding germ line therapies, *i.e.* heritable interventions into the human germ line, both countries have enacted prohibitions. However, France seems to follow a much more liberal path. *E.g.*, in Germany, unlike in France, the prohibition of germ line interventions is part of criminal law. In addition, again in contrast to German law, French law does not ban research on human embryos completely. Such research is indispensable in order to develop safe concepts of future germ line therapies. Moreover, French law, as construed by the Conseil d'État, permits germ line interventions for research purposes aiming at the prevention or treatment of diseases. Aurélie Mahalatchimy considers this interpretation not to be in conformity with the Council of Europe's Biomedicine Convention. Regarding reform efforts, she points to recent amendments to French law on bioethics which aim at facilitating embryo

research to a certain extent. With a view to the protection of patients' biological data, Aurélie Mahalatchimy points to the likely requirement of an authorization to be issued by a special national data protection commission if, and to the extent that, health data is processed in the course of clinical trials or treatments under the 'hospital exemption', 'special needs exemption' or 'compassionate use exemption' clauses.

1.3.3 Switzerland

A distinctive feature of Switzerland's regulatory framework is that the Swiss Federal Constitution enshrines several norms which are expressly related to research involving human beings, reproductive medicine, gene technology, and transplants medicine. All these provisions have a certain bearing on the regulation of genome-edited iPSC-based cell/gene therapies, too. Rainer J. Schweizer, Antonia S. Straden and Hans Peter Bernhard (Chap. 5) give a detailed account on the pertinent constitutional provisions and their meaning. It is equally of note that international law, especially human right treaties adopted within the framework of the Council of Europe (CoE), are highly influential on the Swiss regulatory framework. In the present context, this holds true, *e.g.*, for the Biomedicine Convention and the Data Protection Convention. In addition, the Swiss approach to regulation of genome-edited iPSC-based cell/gene therapies is in many respects aligned with the EU's medicinal products and GMO law. However, there may be slight but notable differences. *E.g.*, the time limit for review of clinical trials applications is only 60 days compared to 90 days which is the regular time line under EU law. As regards germ line therapies, Rainer J. Schweizer, Antonia S. Straden and Hans Peter Bernhard provide a very comprehensive legal assessment carefully distinguishing between the different modalities of such interventions. In the end, Switzerland's law is almost as restrictive as, *e.g.*, German law. Interestingly, the prohibition of germ line interventions can be already inferred from the Swiss Federal Constitution. Additionally, it is also laid down in statutory law, and, similar to Germany, any violation of the prohibition constitutes a criminal offense. However, different from the legal situation in Germany, embryonic stem cells may be derived from supernumerary embryos albeit under very restrictive conditions only. Concerning the treatment of biological data of patients, Rainer J. Schweizer, Antonia S. Straden and Hans Peter Bernhard reveal a complex multi-layered legal framework of data protection rules influenced, apparently, also by EU law. A noteworthy characteristic is that informed consent requirements differ as a function of the kind of material or data at hand (biological material, genetic data, non-genetic health-related data) and the mode of data encryption (uncoded, pseudonymized, anonymized).

1.3.4 United States

The United States (US) is, possibly, the most experienced nation as regards research and development as well as regulation in the field of somatic cell/gene therapies. Kathleen M. Sanzo (Chap. 6) provides an in-depth and enlightening analysis of scientific and regulatory considerations relevant for the design of preclinical studies and early stage clinical trials. In addition, her report outlines the in advance control mechanisms of US law applicable to so-called 'biologics' since genome-edited iPSC-based cell/gene therapy products will be classified into this medicinal products category. An important feature of US clinical trials regulation is that clinical trials, including trials with genome-edited iPSC-based cell/gene therapy products, need to be notified to the competent authority only, *i.e.* if the competent authority does not order a clinical hold, the clinical trial may proceed after expiry of a waiting period of solely 30 days. Another, and unique, characteristic of the US regulatory framework is that manufacturing of medicinal products, including somatic cell/gene therapy products, does not require a special manufacturing licence. In addition, US law provides five programmes facilitating expedited review of applications for marketing authorization. Kathleen M. Sanzo points out that especially the 'Regenerative Medicine Advanced Therapy' (RMAT) programme will be of relevance as regards somatic cell/gene therapies based on genome-edited iPSCs. Importantly, germ line therapies are not expressly prohibited by federal law. However, it is of note that the He Jiankui incident (*supra sub* 1.2.4) prompted US senators to propose a resolution calling for the establishment of global standards for human genome editing. With a view to the protection of patient biological data, it is noteworthy that pharmaceutical companies are not subject to the pertinent health data protection law. Also de-identified health data is not covered by said law. Interestingly, as Kathleen M. Sanzo spells out, "many disclosures of [protected health information] . . . require no authorization by the patient". Concerning so-called secondary research uses of biospecimens (*e.g.*, tissues, cells), consent by the patient concerned is not required if the relevant biospecimen is sufficiently de-identified.

1.3.5 Japan

Japan plays a globally leading role in research and development of regenerative medicine. In particular, the ground-breaking invention of reprogramming somatic cells into iPSCs was made by Shinya Yamanaka at the University of Kyoto who received the Noble Prize in Physiology and Medicine in recognition of this pioneering achievement in 2012. Hanayuki Okura and Akifumi Matsuyama's report (Chap. 7) illustrates that the grant of the Noble Prize was highly influential on the evolution of the Japanese regulatory framework for regenerative medicine. The promotion of regenerative medicine became a top priority of Japanese health policy leading to a completely revised, and partly novel, legal framework designed

specifically to create a regulatory environment supportive of the translation of regenerative medicine research into clinical applications. A distinctive feature of this regulatory framework is its two-track approach. One track is devoted to clinical trials and marketing of regenerative medicinal products ('pharmaceuticals/medical devices law track') whereas the other track is reserved for clinical research and private medical practice applying regenerative medicines ('medical services/medical practitioners law track'). As regards the former track, the revised legal basis also provides for facilitated review procedures aiming at accelerated, conditional and time-limited marketing authorizations. With a view to the latter track, Japan established a tiered risk-based system according to which clinical research, or private medical practice respectively, is classified into three categories of risk depending on whether the risks associated with the particular regenerative medicinal product to be administered to patients are low, medium or high. This classification is decisive for the in advance control mechanism applicable in the individual case. A peculiar and challenging regulatory problem has been how to connect the two tracks in order to improve the broad availability of regenerative medicine. Very intriguing is the case study presented by Hanayuki Okura and Akifumi Matsuyama which concerns allogenic genome-edited iPSC-derived CAR T cells. As regards germ line therapies, only research involving genome editing of fertilized oocytes is outlawed. In contrast, interventions into the germ line for reproductive purposes are not expressly prohibited. However, the disclosure of the human genome editing experiments by He Jiankui in 2018 (*supra sub* 1.2.4) unleashed a political debate in Japan, too, whether germ line therapies within the context of human reproduction should be explicitly banned as well.

1.3.6 Korea

Korea passed a completely new law on advanced regenerative medicinal products in 2019 which entered into force only recently in August 2020. Yu-Cheol Shin (Chap. 8) presents a thorough and concise study of this law as well as of Korea's bioethics law of 2004. The purpose of the new law is the promotion of innovation in the promising field of regenerative medicine without compromising patients' safety. Unsurprisingly, as regards marketing authorizations, the new law also provides for accelerated review procedures to be completed within a time line of 60 days only which is extremely short compared to other countries under review. A distinctive feature of the Korean regulatory framework is that ethical reviews are not carried out by local (*e.g.*, institutional) or regional committees but by a centralized commission established on the national level. Another characteristic of Korea's regulatory framework is the risk-based differentiation of clinical trials with advanced regenerative medicinal products into three classes of risk, depending on whether the risk associated with the trial is low (class C), medium (class B) or high (class A). In contrast to Japan, this tiered risk-based scheme is not determinative of the kind or degree of prior administrative control applicable to the clinical trial at hand. Rather,

the risk classification is of importance as regards the source of the cells to be administered to the subjects or patients respectively. *E.g.*, cells for class A and B trials have to be obtained from an institute established especially for the treatment of cells for regenerative medicine purposes. In addition, clinical trials of gene therapies are limited to certain severe or hitherto untreatable diseases or to cases in which the envisaged gene therapy is likely to be considerably advantageous over existing therapies. It is also of note that the new law on advanced regenerative medicine has established a whole range of new institutions such as, *inter alia*, a commission for political advice on advanced regenerative medicine and a centre for research on the regulation of advanced regenerative medicine. Moreover, treatment of patient biological data is subject to general data protection law as well as special extensive data protection rules laid down in bioethics and advanced regenerative medicine law. As Yu-Cheol Shin points out, transfer of personal data requires express consent in writing by the patient concerned. In addition, the transferred data must be anonymized except in case of a waiver by the patient. Like in other countries under review, germ line therapy is prohibited. This ban explicitly extends to gene therapies applied to embryos, gametes and foetuses.

1.3.7 Comparative Analysis

The last chapter (Chap. 9) provides a comparative analysis of the regulatory frameworks as presented in the country reports (Chaps. 3–8). It identifies certain key regulatory aspects worthwhile of being compared across the different jurisdictions. These aspects are, at a glance, the overall structure of the legal and institutional framework, the regulatory prerequisites for clinical trials, placing on the market and treatments in the absence of prior marketing authorizations, the protection of the patients' biological data, and the regulation of germ line therapies. In particular, as regards the regulation of clinical trials and placing on the market, the comparison focusses on in advance control instruments, consultation mechanisms, timelines, expedited review procedures, manufacturing preconditions, and requirements specifically addressed to the use of genetically modified organisms (GMOs). As a final step, the comparative analysis identifies, albeit somewhat tentatively, 'best regulatory practices' relating to genome-edited iPSC-based somatic cell/gene therapies, germ line therapies and biological data protection. According to this author's (subjective) view, best regulatory practices are, in brief: to establish a three-layered regulatory framework made up of statutes, regulations and guidelines, to adopt regenerative medicine-specific regulation, to confer implementation and enforcement upon centralized public authorities, to avoid undue GMO regulation, to facilitate, or differentiate, in advance control mechanisms applicable to clinical trials (*e.g.*, by requiring, as a function of the risks involved, prior notification instead of prior authorization), to provide for early consultation mechanisms, to enact special marketing authorization procedures (*e.g.*, expedited review procedures resulting in conditional or time-limited authorizations), to permit treatment of patients prior to

marketing authorization of the medicinal product concerned, albeit in exceptional cases only, to abolish the requirement of a manufacturing licence, to differentiate informed consent requirements as regards uses of patient biological data, and to impose a moratorium on germ line therapies.

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Chapter 2
Introduction to Genome Editing in Induced Pluripotent Stem Cells, Gametes, and Embryos

Tobias Cantz

Abstract This chapter discusses recent findings and technological advances in stem cell biology, in gametogenesis, in genetic engineering and in the potential treatment of hereditary diseases by means of gene and cell therapy-approaches. Important scientific mile stones for human germline interventions include the understanding of reprogramming approaches that drive terminally differentiated somatic cells into pluripotent stem cells, exhibiting all major characteristics of embryonic stem cells. Furthermore, recent advances in the derivation and differentiation of pluripotent stem cells paved the way for a clinical application of such derivatives and ask for the possibility to generate either female and/or male gametes from such cells for reproductive purposes. Also, recent advances in genetic engineering, such as the CRISPR/Cas technology, fuelled the discussion about safety and efficacy of germline interventions in the foreseeable future. Finally, two scenarios are discussed to challenge the current normative view on targeted genome interventions during in vitro fertilization applications for couples suffering from hereditary diseases.

2.1 Reprogramming and Induced Pluripotent Stem Cells

In 2012 the Nobel Prize in Physiology or Medicine was awarded to John B. Gurdon and Shinya Yamanaka for their ground-breaking work on the reprogramming of somatic cells. When John B. Gurdon performed his seminal experiments in the 1960ies by transferring somatic cells' nuclei from tadpoles into enucleated frog oocytes, he was able to demonstrate that the resulting entities exhibited all hallmarks of totipotent one-cell-embryos that were able to further develop into tadpoles and

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H.-G. Dederer, G. Frenken (eds.), *Regulation of Genome Editing in Human iPS Cells*, https://doi.org/10.1007/978-3-030-93023-3_2

subsequently into viable, fertile frogs.[1] The birth of sheep Dolly in the late 1990ies[2] finally proved that the reprogramming of somatic cells towards totipotency is also achievable in mammals and, nowadays, live born somatic cell nuclear transfer (SCNT)-derived animals have been reported for a variety of species including mice, pigs, cattle. SCNT embryos from human somatic cells could be derived as well and SCNT-derived human embryonic stem cells were propagated as infinite cells line in various laboratories.[3] In essence, this approach would enable the generation of pluripotent stem cells from patients' somatic cells for further disease-related research or even therapeutic applications. However, the concept of such SCNT-derived human embryonic stem cells was discussed very controversially even before it was achieved in 2013, because the quest for patient-derived pluripotent stem cells was undoubtedly of high relevance for various approaches in regenerative medicine but the procedure was involving the destruction of human pre-implantation embryos.

The work of Shinya Yamanaka was focusing on a very different approach to generate patient-derived pluripotent stem cells. He was seeking for transcription factors that were able to reprogram the gene regulatory network of somatic cells (such as fibroblasts) into that of pluripotent stem cells and he was able to demonstrate that a set of 4 transcription factors (Oct4, Sox2, Klf4, c-Myc) was sufficient to reprogram somatic cells into induced pluripotent stem cells (iPSCs). Following the publication of his 2006 paper,[4] the matter of full pluripotency of such iPSCs was debated quite controversially, because the published experiments provided a lot of evidence for the successful establishment of pluripotency, as demonstrated by the presence of various derivatives from all three germ layers in teratoma assays as well as in mouse chimera experiments. However, the ultimate criterion, i.e. the contribution to germ cells, was not shown in that 2006 publication. It took his team one more year to demonstrate that these iPSCs were indeed fully pluripotent and successfully contributed to germ cells in a more fine-tuned experimental setting.[5]

From 2007 onwards, a set of further publications demonstrated the contribution of iPSCs to gametes in mouse chimera formation studies and the level of that germline chimerism was regarded as indicator for the overall quality of (reprogrammed) pluripotent stem cells. Basically, the chimerism obtained from "good" iPSCs was about 30–50% and included gametes, while the chimerism obtained from "poor" iPSCs was low and excluded the contribution to the germ-line. An even more discriminative approach is to perform the chimera experiments with tetraploid embryos, i.e. embryos that exhibit a tetraploid chromosomal content resulting in a rather poor developmental capacity in comparison to (good) diploid embryos with normal chromosomal content. Such tetraploid embryos could form a proper

[1] Gurdon (1962).

[2] Wilmut et al. (1997).

[3] Tachibana et al. (2013); Johannesson et al. (2014).

[4] Takahashi and Yamanaka (2006).

[5] Okita et al. (2007).

trophectoderm, but would specify only a rudimentary inner cell mass at the blastocyst stage.[6] Importantly, these few inner cells would still be able to guide the further steps of embryonic (post-gastrulation) development after implantation, but only the complementation with intact diploid pluripotent stem cells, such as "good" iPSCs, would result in proper development and subsequently in live-born pups.[7] Studies applying such tetraploid embryo complementation approaches were able to identify distinct epigenetic signatures of fully reprogrammed iPSCs[8] and to suggest most suitable stoichiometric ratios[9] of the four reprogramming factors (Oct4, Sox2, Klf4, c-Myc), and provided proof-of-concept that gene corrected iPSCs are stable enough to correct otherwise life-threatening genetic defects.[10]

2.2 iPSC-Based Therapies

Particular attention is paid to the first clinical study in which iPSCs were used to replace retinal pigment epithelial cells in macular degeneration. Initially, autologous (patient's own) iPSCs were generated and further differentiated in vitro, before they were re-transplanted into the retina of one eye. The entire procedure was safe in the first patient, but in the second application, the safety analyses before the cell transplantation revealed considerable chromosomal abnormalities in that patient's iPSC derivatives.[11] Thus, the concept of autologous cell transplantation was questioned in this trial and additional efforts were initiated to establish allogeneic cell therapies with immunocompatible cells. These cells would be made available by an iPSC biobank of cells that would fit the vast majority of the Japanese population. This specific example shows that genetically intact iPSC grafts can be generated in principle, but that most rigid quality controls and safety analyses are necessary to assess the avoidable risks and side effects of such cell therapies. This problem becomes even more serious and more complex if patient-iPSCs may need to be genetically corrected in order to repair a genetic defect on which the disease is based.[12]

The adaptation of the CRISPR-Cas technology[13] for precise genome editing was awarded with the Nobel Prize for Chemistry in 2020 and is already being tested in the first clinical studies. For example, T cells (e.g. as PD-1 knockout T cells) are modified in vitro in such a way that they enable personalized T cell-mediated tumour

[6] Eakin et al. (2005).
[7] Kang et al. (2009); Zhao et al. (2009).
[8] Stadtfeld et al. (2010).
[9] Carey et al. (2011).
[10] Wu et al. (2011).
[11] Blau and Daley (2019).
[12] Blau and Daley (2019).
[13] Jinek et al. (2012).

immunotherapy after transplantation.[14] So far, however, the spectrum of possible side effects of gene modification has not yet been fully and completely assessed. The two main risks are currently assumed as: (i) the inaccurate binding of the Cas9 enzyme to the desired gene locus and the change in other target sequences (off-target effects), which can, however, always be better determined using in silico algorithms; (ii) an unwanted and unspecific genetic integration of the DNA repair templates during the process of homology-driven repair (HDR).

With regard to the application of CRISPR-Cas9-mediated gene editing in iPSCs, the technology for the analysis of iPSC subclones has fortunately advanced far enough by now allowing for relatively easy identification of corrected iPSCs. The full genome analysis to be expected as a routine procedure in the future can then analyse the genomic integrity of the modified iPSCs (genotoxicity) and the quality of the genome modification (phenotoxicity) with sufficient certainty. For a possible immunotoxicity, i.e. an immune response against the iPSC derivatives or specifically against the protein expressed by the CRISPR-Cas9 correction, examinations must be carried out in suitable preclinical models or early clinical study phases. Recently, the company Fate Therapeutics announced the first FDA-approval of a genetically engineered iPSC-derived natural killer (NK-) cell transplant[15] to fight B-cell malignancies as monotherapy or in combination with a monoclonal antibody therapy such as rituximab.

Although this scenario of individual autologous iPSC-based gene therapy appears to be complex and possibly difficult to navigate through the channels of medicinal products regulation, there is also a tremendous development in the area of the automation and miniaturization of cell culture and genetic engineering techniques. It is currently unpredictable whether these technical challenges can be transferred to the iPSC field relatively quickly, but the findings to date regarding the handling of the iPSCs and their genomic manipulation at least suggest that these work steps could be automated in micro-robotic systems. If such cells become actually available for clinical trials and for a commercially usable application in the patient, these cell transplants are to be classified as so-called ATMPs (Advanced Therapy Medicinal Products). ATMPs include products for gene therapy, cell therapy and tissue engineering and are assessed by a number of different supervisory authorities for approval within Europe. As mentioned above, the question of possible genetic changes, which can be answered with the means of full genome sequencing in accordance with the current state of knowledge, is of great importance. This might raise the fundamental question as to whether state authorities or government agencies are allowed to get access to genome sequences of patient materials and whether patients can also prohibit the transmission of their individual genome information.

[14] Stadtmauer et al. (2020).

[15] Zhu et al. (2020).

2.3 iPSC-Derived Gametes

Recent biological advances facilitate the generation of induced pluripotent stem cells (iPSCs) from various freshly isolated somatic cell sources. Furthermore, iPSCs can also be obtained from frozen cell preparations that were stored in biobanks or in biomedical research labs. One of the hallmarks of pluripotent stem cells is their capability to differentiate into all cell types of the body, including germ cells. In this regard, recent publications demonstrated that human pluripotent stem cells could give rise to immature germ line cells but it remains unclear how and in which time-frame functional gametes could be obtained from human pluripotent stem cells such as embryonic stem cells as well as induced pluripotent stem cells.[16] So far, stem cell derived germ cells rather represent a stage like primordial germ cells that have the ability to enter into meiosis and give rise to haploid, gamete-like cells. However, the further molecular steps of the meiotic division and the generation of functional gametes were not yet achieved with cells of human origin. Of note, data from 2006 suggested that in mice functional sperm was derived during in vitro differentiation of murine embryonic stem cells,[17] but this data was not backed-up by other independent reports. A similar report on the derivation of sperm from human embryonic stem cells, however, was retracted a few years later.[18]

One of the major issues during the formation of gametes is the erasure of paternal and maternal imprints and the subsequent differential imprinting of female and male gametes. So far it is not easily assessable to which extent the full erasure of the somatic cells' imprints can be achieved during gametogenesis from iPSCs and how the respective imprints can be induced during female or male gametogenesis. Moreover, it is not yet elucidated whether pluripotent stem cells from male individuals (carrying X- and Y- chromosomes) could efficiently give rise to haploid sperm (either one X- or one Y-chromosome) and to haploid eggs (one X-chromosome). Furthermore, iPSCs from female individuals (carrying two X-chromosomes) could give rise to oocytes but could not readily give rise to sperm, because some important genes for spermatogenesis are encoded on the Y-chromosome and it needs to be elucidated to which extent the main regulatory factors encoded by these genes can be substituted during gametogenesis by additional genetic interventions. At this stage the reasonable assumption remains that such in vitro generated artificial gametes will harbour subtle epigenetic misregulations of relevant transcriptional networks yielding in an impaired functionality of the respective gametes, which might cause severe disturbances during embryogenesis.

Nevertheless, from today's perspective the iPSC-based generation of oogonial precursor cells and their subsequent transplantation in the ovaries of infertile females might become a therapeutic strategy to overcome infertility after radiation or chemotherapy during the therapy of cancer in young women. Similarly, spermatogonial

[16] Saitou and Miyauchi (2016).
[17] Nayernia et al. (2006).
[18] Nayernia et al. (2009).

stem cells could be derived from iPSCs and transplanted into the testes of men suffering from infertility after aggressive tumor therapies.[19] Once functional human germ cells can be derived from iPSCs in a direct in vitro approach such artificial gametes become applicable in reproductive medicine, which would urge the need for setting up a respective normative framework.[20] Besides legal and ethical considerations, biological safety issues due to prolonged in vitro cultivation and putative genetic modifications need to be assessed and implemented in new normative regulatory frameworks.

2.4 Gene Correction in iPSCs Targeting Hereditary Diseases

New technologies for a precise repair of genetic lesions take advantage of the endogenous DNA repair machinery that uses homologous DNA-strands as template during the correction of the respective genetic sequence.[21] This homology-directed repair (HDR) mechanism is greatly facilitated after induction of a DNA double strand break in the vicinity of the region to be corrected. Older approaches like Zink Finger Nucleases (ZFNs) or Transcription Activator-Like Effector Nucleases (TALENs) need laborious work steps ensuring the sequence-specific nuclease activity and are limited by their low efficacy to bi-allelic correction in the targeted cells. More recently, a defence mechanism protecting bacteria from foreign genetic elements was discovered. Bacterial DNA contains so-called Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), in which foreign DNA can be integrated. These exogenous DNA elements can be cleaved by a CRISPR-associated (Cas) endonuclease and confer immunity against a subsequent infection by the respective phage or plasmid. Importantly, this CRIPSR/Cas system can also be expressed in plant or animal cells and allows an easy and highly efficient generation of DNA double strand breaks, which greatly facilitates the aforementioned precise genome engineering approaches. Recent publications suggest that modifications of the Cas9 nuclease itself or the use of other Cas orthologous may enhance the target specificity and may further reduce off-target cutting risks.

All of these HDR-mediated gene modification approaches need cell division steps (i.e. the occurrence of the G2 or S-phase of the cell cycle), and subsequent selection strategies are very helpful to identify correctly targeted cells that lack unintended off-target mutations. Therefore, the application of precise genome engineering technologies is most suitable for the correction of (clonally) expandable cells, from which an aliquot can be used for detailed genetic analyses, but it is rather inefficient in non-expandable somatic stem cells. Therefore, today, the strength of

[19] Mulder et al. (2016).

[20] Advena-Regnery et al. (2018).

[21] Cornu et al. (2017).

the CRISPR/Cas mediated gene repair lies in the correction of pluripotent stem cells and, with some limitations, in the genetic manipulation of early embryos.

Most hereditary diseases are manifested as rare diseases already in the childhood and current concepts of molecular medicine aim to generate patient-specific cell transplants that correct an impaired organ function without need of long-term immunosuppressive treatment, which is considered as a major limitation for paediatric transplantation therapies. The recent advances in the generation of patient-specific iPSCs provide a promising resource for such autologous cell transplants, but in the case of hereditary diseases the underlying genetic defect must be repaired before such transplants can be used in a sustained therapeutic approach. Even if it is speculative at this time, there are good reasons to assume that for a number of life-threatening hematologic, immunologic or metabolic disorders a curative tailored cell transplant can be generated exploiting the CRIPSR/Cas- and iPSC-technology in a combined somatic gene and cell therapy approach.

However, the patients' descendants may also suffer from the respective disease, which is also encoded in their germ cells. Currently, it seems challenging to correct germ cells with a precise genome engineering approach,[22] because this technology needs active cell division and selection strategies for repaired cells that carry the correct genetic sequence and that lack off-target mutations. But the CRISPR/Cas-corrected iPSCs that were generated for patient-specific somatic cell transplantion may also be differentiated into intact germ cells in the upcoming future. At present, a transmission of the genetic defect to subsequent generations could be prevented only by in vitro fertilisation (IVF) technology combined with pre-implantation genetic diagnostics (PGD) that allows the identification of unaffected embryos. However, in the rare case in which both parents suffer from the same recessive disorder all of their gametes will carry the mutation and all embryos will carry two mutated alleles. In this case, a direct CRISPR/Cas-mediated gene correction approach in early embryos (pronuclear stage or one-cell-stage) might be considered as an option to generate healthy descendants of the respective couple. In other situations, where unaffected embryos could be identified by PGD, CRIPSR/Cas-mediated gene correction might become an alternative to the disputed PGD-based selection of healthy embryos, once the technology becomes similarly safe and reliable as normal cleavage or cell division steps in fertilized embryos. But, such CRISPR/Cas-mediated embryo manipulation approaches might be also exploited in enhancement applications.

[22] Mulder et al. (2016).

2.5 Scenarios

In the following scenarios, the disease cystic fibrosis (CF) is explored as an example which is of high clinical relevance in Western countries with ~80,000 cases and might become the subject of germline editing measures in the future.[23] Cystic fibrosis is caused by sequence variations in the CFTR gene, leading to serious malfunctions in the lung, liver, and intestine.[24] The hereditary transmission is autosomal recessive which means that both alleles of the CFTR gene must be mutated to cause the disease-affected genotype. In the current debate on germline interventions CF is discussed as one example where a constellation might occur in which both partners are affected from a recessive disease. In this constellation, all gametes would carry the genetic mutation, and without genetic corrections of the gametes, no healthy descendants can be born. However, the impact of such a scenario is disputable because that particular constellation is obviously quite rare. Furthermore, the debated lack of any therapeutic alternative might be challenged by innovative treatment options with new drugs or somatic gene therapy approaches, which would supersede germline intervention as the only treatment option.

However, a couple consisting of two healthy carriers, each carrying one mutated CFTR allele, would be a more frequent situation and would be actually more relevant for the ethical debate, because under these circumstances alternative options like pre-implantation genetic diagnostics (PGD) could be discussed (Fig. 2.1).

2.5.1 Scenario 1: Gene Editing at the Endogenous Gene Locus of CFTR

When pre-implantation genetic diagnostics (PGD) is applied during in-vitro fertilization (IVF) procedures for couples affected from known hereditary diseases, embryos devoid of known genetic mutations were selected and the remaining embryos were discarded, which raises considerable ethical concerns. The current state-of-the-art for gene editing approaches in early embryos would also call for pre-implantation genetic diagnostics in order to assess the efficacy and safety of the intervention prior to the implantation of the most favourable selected embryos. However, future advances of the technology might minimize the unintended off-target effects and maximize the efficacy of the targeted gene editing approach during an IVF procedure for couples affected by a hereditary disease. In such a scenario, one could suggest that the overall risk of genome editing interventions is not adding too much to the natural mutation rate during embryogenesis and, therefore, is sufficiently small. In this case, the gene correction-associated risks are

[23] Griesenbach et al. (2015); Prakash et al. (2016).

[24] Cutting (2015).

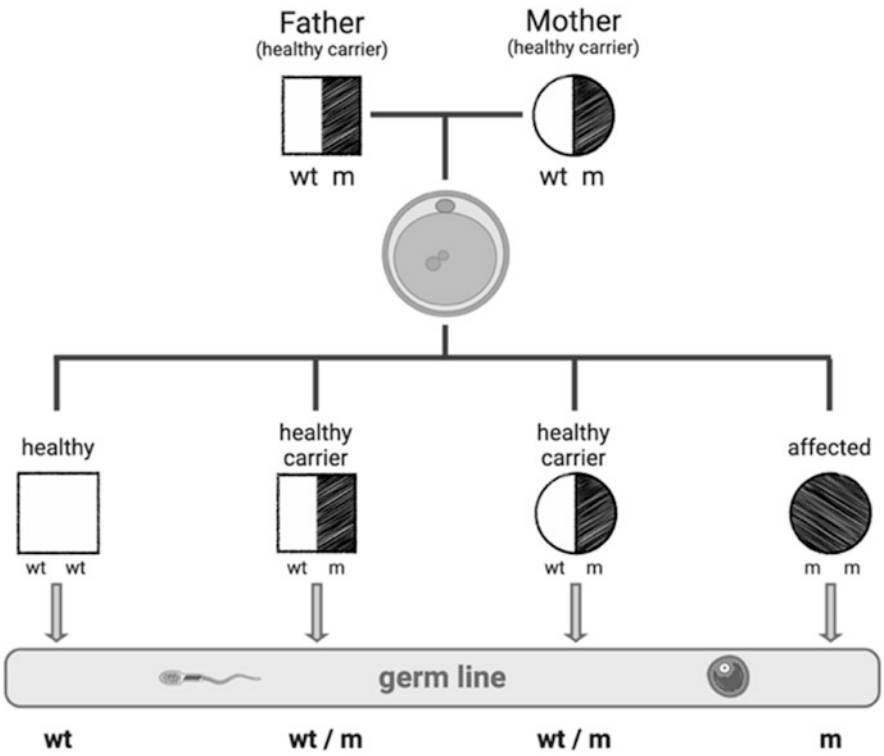

Fig. 2.1 Genetic pedigree of an autosomal recessive disorder. Both parents carry one mutated (m) and one healthy wild-type (wt) allele. One of these is passed during gametogenesis and subsequent fertilization to the next generation. In 1 out of 4 cases, both wt-alleles were inherited (healthy individual), in 2/4 cases one wt- and one m-allele were inherited (healthy carrier) and in 1/4 both m-alleles were inherited (affect individual). The germ cells of this generation would, then, transmit one of the parental alleles, either a wt- or m-allele in the carrier case, a wt-allele in the case of the healthy individual, or a m-allele in the case of the affected individual

considered as the probability of any unintended genomic mutation caused by the CRISPR/Cas technique that adds to the natural mutation rate during gametogenesis and early embryo development. But more complex IVF procedures like intracytoplasmic sperm injection (ICSI) or other interventions, which were routinely performed, would require considerable in vitro propagation of the gametes and early embryos, and often would be performed with gametes from (at least) one elderly partner exhibiting increased levels of genetic mutations more frequently than gametes from healthy, fully fertile couples. Overall, it could be assumed that envisioned improvements of the CRISPR/Cas9 technology (or similar superior approaches) for gene editing will result in an off-target mutation rate that would not significantly deviate from the overall mutation rate in complex procedures of assisted reproductive medicine.

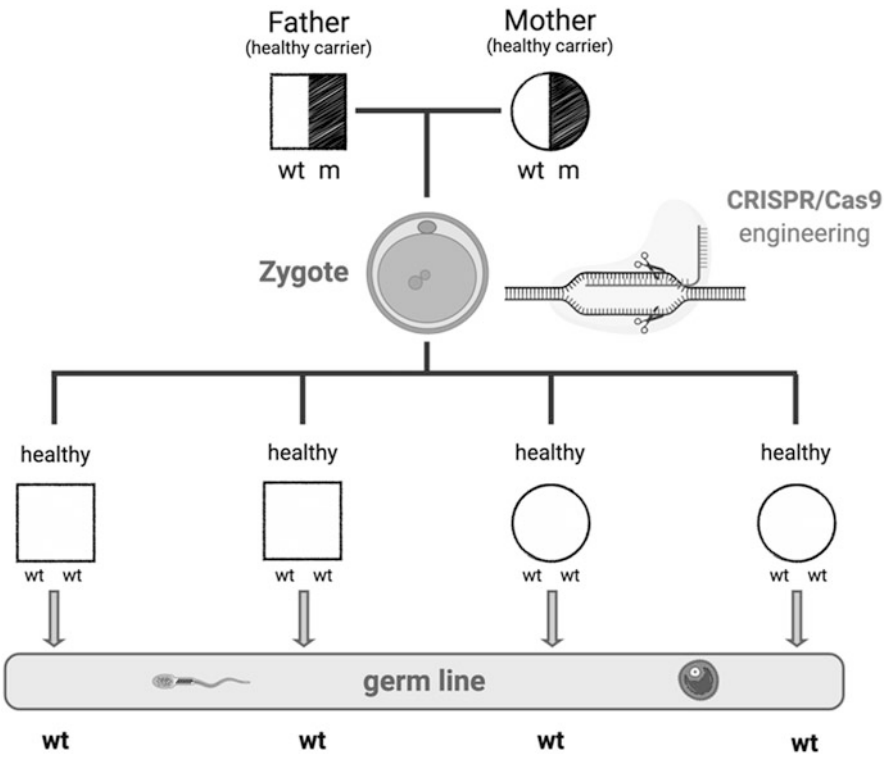

Fig. 2.2 Scenario 1—CRISPR/Cas9-mediated gene editing at the endogenous CFTR gene locus. Both parents carry one mutated (m) and one healthy wild-type (wt) allele. A gene editing approach during the early fertilization steps might allow the repair of the respective m-allele into a wt-allele. Thus, all descendants would carry only wt-alleles and could be considered as healthy individuals

In the context of germline therapies for autosomal recessive diseases like Cystic Fibrosis (CF), a CRISPR/Cas gene editing approach may be used to repair the underlying defect in the CFTR gene directly at the endogenous DNA locus of all in vitro generated human embryos of an affected couple. For this purpose, the CRISPR-Cas complex is injected into the pronucleus stage of the zygote and the intervention might target all alleles, whether mutant or not, by overwriting the respective sequence into the wild-type sequence of the CFTR gene. In this scenario, all cells of the developing embryo would produce the wild-type form of the CFTR gene and the mutant allele would be eliminated from carrier embryos and also from all future descendants (Fig. 2.2).

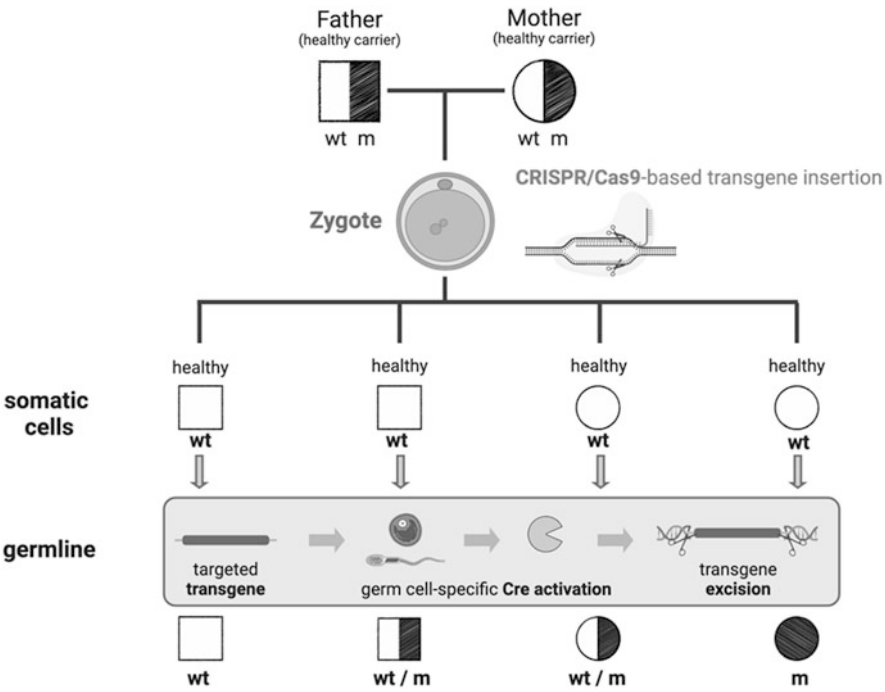

Fig. 2.3 Scenario 2—one-generation germline therapy. Both parents carry one mutated (m) and one healthy wild-type (wt) allele. A complex gene editing approach during the early fertilization steps might allow the insertion of a transgene cassette carrying a cDNA of the wt-allele to be expressed in a tissue-specific pattern in the respective somatic cells of the descendants. Furthermore, the transgene cassette drives the expression of a Cre-recombinase gene in all gametes, which would mediate the excision of the transgene cassette from the descendants' germline. Thus, the first generation descendants would express wt-CFTR gene products in their somatic cells, but would keep the parental allele-related inheritance of the m- and wt-alleles in the germline

2.5.2 Scenario 2: One-Generation Germline Therapy

As a much more complex form of gene therapy, which one could call "one-generation germline therapy", a transgenic cassette could be introduced into the genome of all embryos. Here, the CRISPR/Cas (or a similar superior) approach would be used to insert a transgene cassette into a favourable genetic region, such as the AAVS1 safe harbour locus,[25,26] of all in vitro fertilized embryos into the pronucleus stage of the zygote, while the endogenous CFTR gene locus remains unaffected. It would therefore be an additive gene edition approach (Fig. 2.3).

[25] AAVS1: adeno-associated virus integration site 1 locus in the first intron of PPP1R12C gene; The AAVS1-locus is a well-established safe-harbour genomic region that allows the expression of delivered DNA sequences without relevant adverse effects for the host organism.

[26] Sadelain et al. (2011).

Likewise to Scenario 1, it is assumed that the gene addition into the AAVS1 locus is safe and efficient, resulting in a rate of unintended on- or off-target effects that would not deviate too much from the mutation rate during other complex IVF procedures. The inserted transgene cassette would not only contain the wildtype CFTR-cDNA with its tissue-specific promoter sequence, but also a Cre recombinase gene,[27,28] which is controlled by a germline specific promoter. The application of this transgene cassette means that CFTR gene products will be expressed from the wildtype copy of the CFTR gene in a tissue-specific manner. However, during gametogenesis, the transgene cassette, flanked by two loxP-sites, is excised from the genome by the Cre recombinase. This intervention would remove the exogenous transgene cassette from the germ cells, with the exception of a slight footprint in form of a few additional functionally inactive DNA nucleotides after recombination and, thus, future descendants remain unaffected from the genome editing intervention.

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[27] Cre recombinase: Cre Recombinase is a Type I topoisomerase from bacteriophage P1 that catalyzes the site-specific recombination of DNA between loxP sites.

[28] Abremski and Hoess (1984).

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Chapter 3
Regulation of Genome Editing in Human iPS Cells: Germany

Gregor Frenken and Hannah Lüttge

Abstract Until 2021, ten GTMPs and one CTMP have been authorised in the EU and fifteen further are expected to become available by 2023—an augmentation that underlines the relevance of the regulatory framework for combined gene/cell therapy in the EU and, in particular, in Germany as one of its Member States. The present chapter aims at describing the regulation of genome-edited human iPS cells to be differentiated into somatic cells for autologous re-transplantation. Departing from Germany's constitution as a federal state and its being a Member State of the EU, the key actors in the field of pharmaceutical regulation (EMA, PEI) are presented and their interplay in the multi-level system is analysed. The regulatory processes governing the development, manufacture, marketing and application of ATMPs is scrutinised. Special attention is paid to the EU's schemes aimed at fostering innovation and guaranteeing the availability of medicinal products required for public health as well as to the possibilities of making available medicinal products without marketing authorisation. The analysis shows that, integrated into the European system, the German regulatory framework strives for maintaining high standards, while at the same time securing scientific and economic competitiveness and best treatment for the individual patient.

Abbreviations

ATMP	Advanced Therapy Medicinal Product
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CTMP	Somatic Cell Therapy Medicinal Product
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice

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H.-G. Dederer, G. Frenken (eds.), *Regulation of Genome Editing in Human iPS Cells*, https://doi.org/10.1007/978-3-030-93023-3_3

GMO Genetically Modified Organism
GMP Good Manufacturing Practice
GTMP Gene Therapy Medicinal Product
PEI Paul Ehrlich Institute

3.1 Introduction

The EU in general and Germany in particular play an important role in the field of gene and cell therapy. As an approach to the topic, an overview of GTMPs and CTMPs available within the EU and of current clinical research activities shall be given, before briefly outlining the historical development of the regulatory framework for ATMPs in Germany and the EU.

3.1.1 Gene Therapy and Cell Therapy in Figures

Until February 2021, ten GTMPs and one CTMP have obtained a marketing authorisation which is valid throughout the EU and is granted in the centralised procedure by the European Commission on the advice of the EMA. One of these marketing authorisations has expired, the rest are still valid (Tables 3.1 and 3.2).

By 2023, the German Association of Research-Based Pharmaceutical Companies expects fifteen further gene therapies to become ready for authorisation, eight of which are based on T cells.[1] Among the envisaged indications are haemophilia B, spinal muscular atrophy, choroideremia and juvenile macula degeneration. However, the vast majority are oncologic gene therapies.

From 1st January 2014 to 30th June 2019, 323 clinical trials with ATMPs were initiated in the EU. 67 dealt with *in vivo* gene therapy, 110 with *ex vivo* gene therapy, 112 with cell therapy and 24 with tissue engineering. With a total of 83 clinical trials during this period, Germany is fourth in clinically investigating advanced therapies in the EU.[2]

3.1.2 Historical Development of ATMP Legislation

Legislation on medicinal products is a typical field of policing law. Its origins date back to the mediaeval regulation of pharmacies.[3] However, until the beginning of the 1960s, only scattered provisions across various acts existed in Germany. The

[1] Verband Forschender Arzneimittelhersteller e.V. (2020).
[2] Alliance for Regenerative Medicine (2019), p. 3.
[3] Freund (2017), Vorbemerkung vor § 1, par. 1–2.

Table 3.1 Approved Gene Therapy Medicinal Products[a]

Name	Holder of the marketing authorisation (MA)	Date of MA	Indication
Glybera[b]	uniQure biopharma B.V.	25.10.2012	Hyperlipoproteinemia type I
Imlygic	Amgen Europe B.V.	16.12.2015	Melanoma (not resectable, metastasised)
Strimvelis	Orchard therapeutics (Netherlands) BV	26.05.2016	Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)
Kymriah	Novartis Europharm Limited	23.08.2018	B-Cell Acute Lymphoblastic Leukaemia (ALL); Diffuse Large B-Cell Lymphoma (DLBCL)
Yescarta	Kite Pharma EU B. V.	23.08.2018	B-Cell Lymphoma (DLBCL and PMBCL)
Luxturna	Novartis Europharm Limited	22.11.2018	Leber Congenital Amaurosis; Retinitis Pigmentosa
Zynteglo	Bluebird bio (Netherlands) B.V.	29.05.2019	Beta-thalassemia
Zolgensma	Novartis gene therapies EU Limited	18.05.2020	Spinal muscular atrophy (type 1)
Tecartus	Kite Pharma EU B. V.	14.12.2020	Mantle cell lymphoma
Libmeldy	Orchard Therapeutics (Netherlands) BV	17.12.2020	Metachromatic Leukodystrophy (MLD)

[a]Cf. Paul-Ehrlich-Institut (2021a); Verband Forschender Arzneimittelhersteller e.V. (2021)
[b]As the holder of the marketing authorisation for Glybera did not apply for a renewal, the marketing authorisation has expired in 2017

Table 3.2 Approved Somatic Cell Therapy Medicinal Products[a]

Name	Holder of the marketing authorisation (MA)	Date of MA	Indication
Alofisel	Takeda Pharma A/S	23.03.2018	Perianal fistulas in Crohn's disease

[a]Cf. Paul-Ehrlich-Institut (2021b); Verband Forschender Arzneimittelhersteller e.V. (2021)

Medicinal Products Act *(Arzneimittelgesetz)* adopted in 1961 was the first comprehensive codification. It imposed an authorisation requirement for the manufacture of medicinal products outside pharmacies. Newly developed medicinal products had to be notified, but were not controlled for quality, safety and efficacy.[4]

The thalidomide scandal[5] already pointed out the deficiencies of the new legislation at the time of its adoption. The EEC reacted in 1965 by enacting its first

[4]Deutsch and Spickhoff (2014), p. 968; Freund (2017), Vorbemerkung vor § 1, par. 4; Kügel (2016a), par. 9–10; Pfohl (2020), Vorbemerkung, par. 1.

[5]In Germany known as the *Contergan-Skandal*.

directive on medicinal products introducing an authorisation requirement for the placement on the (common) market of medicinal products, which should only be granted after a control of quality, safety and efficacy. Eleven years later, and only after another European directive had been adopted, Germany incorporated the requirement of a marketing authorisation into the Medicinal Products Act.[6]

In the twenty-first century, the EU's regulatory framework for medicinal products was consolidated and further improved.[7] A milestone for innovative therapies was the adoption of the Regulation on ATMPs in 2007, which made the EU a pioneer in this field. No other region in the world has granted more marketing authorisations for ATMPs than the EU, which can be understood as a first sign of the success of the regulatory framework.[8]

3.2 Genome Editing in Human iPS Cells: An Overview of the Regulatory Framework

The regulatory framework for combined gene/cell therapy in Germany is complex. This is due to Germany's constitution as a federal state and its being a Member State of the EU. In order to outline the legal framework and describe the relevant actors in the field of pharmaceutical products and gene technology, first, the distribution of legislative and administrative powers within the Federal Republic of Germany shall be scrutinised. Second, a detailed analysis of the distribution of powers between the EU and its Member States is indispensable for explaining, third, the actual use said bodies make of their respective powers.

3.2.1 The National Framework of the Federal Republic of Germany

Germany is constituted as a federal state and governed by its constitution, the Basic Law.[9] In principle, the *Länder* exercise state powers:[10] the legislative, executive and

[6] Freund (2017), Vorbemerkung vor § 1, par. 5; Kügel (2016a), par. 10–14, 16–17, 20; Pfohl (2020), Vorbemerkung, par. 2.

[7] Kügel (2016a), par. 18.

[8] Alliance for Regenerative Medicine (2019), p. 1.

[9] Basic Law for the Federal Republic of Germany *(Grundgesetz für die Bundesrepublik Deutschland)* in the revised version published in the Federal Law Gazette Part III, classification number 100-1, last amended by Article 1 of the Act of 28 March 2019 (Federal Law Gazette I p. 404). An English translation is available at https://www.gesetze-im-internet.de/englisch_gg/englisch_gg.pdf (accessed 25 Feb 2021).

[10] Basic Law, Art. 30.

judicial powers are vested in the *Länder* insofar as the Basic Law does not confer legislative, executive or judicial power upon the Federation.[11]

Nevertheless, the legislative power for "the law on pharmacies, medicines, medical products, drugs, narcotics and poisons"[12] and for "analysis and modification of genetic information"[13] is attributed to the Federation as a matter of concurrent legislative power, i.e. the *Länder* have power to legislate as long as and to the extent that the Federation has not exercised its legislative power.[14] Based on this allocation of legislative power, the Federation has enacted the Medicinal Products Act[15] and the Genetic Engineering Act.[16] In consequence, the *Länder* are barred from legislating on these matters.

However, according to the general allocation of executive power, execution and enforcement of both acts are carried out by the *Länder* in their own right.[17] Nonetheless, as far as the approval of medicinal products for human use, the authorisation of clinical trials and certain actions of pharmacovigilance are concerned, the Medicinal Products Act is executed by two federal higher authorities:[18] the Federal Institute for Drugs and Medical Devices and the Paul Ehrlich Institute.[19] The latter is competent for the regulation of ATMPs.[20] As regards the contained use of GMOs, the Genetic Engineering Act is executed by the *Länder*. The Federal Office of Consumer Protection and Food Safety is the competent federal higher authority, though, as far as the placing on the market of GMO products is concerned.[21]

[11] Basic Law, Art. 70(1), 83, 92.

[12] Basic Law, Art. 74(1) No. 19.

[13] Basic Law, Art. 74(1) No. 26.

[14] Basic Law, Art. 72(1).

[15] Medicinal Products Act *(Arzneimittelgesetz)* in the version published on 12 December 2005 (Federal Law Gazette Part I p. 3394), last amended by Article 11 of the Act of 6 May 2019 (Federal Law Gazette I p. 646). An English translation is available at https://www.gesetze-im-internet.de/englisch_amg/englisch_amg.pdf (accessed 25 Feb 2021).

[16] Genetic Engineering Act *(Gentechnikgesetz)* in the version published on 16 December 1993 (Federal Law Gazette Part I p. 2066), last amended by Article 21 of the Act of 20 November 2019 (Federal Law Gazette I p. 1626). Regrettably, only an unauthorised English translation of the version of 2003 is available at http://web.uni-frankfurt.de/si/gentech/GenTGengl10-95c.pdf (accessed 25 Feb 2021).

[17] Cf. Basic Law, Art. 83.

[18] Cf. Basic Law, Art. 87(3).

[19] Medicinal Products Act, § 77(1).

[20] Medicinal Products Act, § 77(2).

[21] Cf. Genetic Engineering Act, § 31.

3.2.2 The Supranational Framework of the European Union

Germany is a Member State of the EU. In accordance with the Basic Law,[22] Germany has transferred sovereign powers to the EU by signing and ratifying the Treaties on which the EU is based. These are currently the Treaty on European Union[23] and the Treaty on the Functioning of the European Union.[24]

The EU and the Member States share competence for "common safety concerns in public health matters",[25] i.e. both the EU and the Member States have legislative power concerning "measures setting high standards of quality and safety for medicinal products and devices for medical use",[26] which comprises setting the standards themselves as well as administrative procedures.[27] Similar to the concept of concurrent legislative power in Germany, the Member States only have the power to legislate to the extent that the EU has not exercised its competence;[28] they are also barred from heightening the standards of quality and safety for their respective jurisdiction.[29] Furthermore, the EU and the Member States share competence for the "internal market":[30] the EU is entitled to "adopt the measures for the approximation of the provisions laid down by law, regulation or administrative action in Member States which have as their object the establishment and functioning of the internal market."[31]

Based on both competences—the specific one for medicinal products and the generic one for the internal market—,[32] the EU has adopted various legal acts. Most relevant in the field of pharmaceutical products are the Directive on the Community

[22] Basic Law, Art. 23(1).

[23] Consolidated Version of the Treaty on European Union [2016], OJ C 202, 7.6.2016, p. 13 (TEU), available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:12016M/TXT&from=EN (accessed 25 Feb 2021).

[24] Consolidated Version of the Treaty on the Functioning of the European Union [2016], OJ C 202, 7.6.2016, p. 47 (TFEU), available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:12016E/TXT&from=EN (accessed 25 Feb 2021).

[25] TFEU, Art. 4(2)(k).

[26] TFEU, Art. 168(4)(c).

[27] Schmidt am Busch B (2016), par. 62.

[28] TFEU, Art. 2(2).

[29] Lurger (2018), par. 52; Schmidt am Busch (2016), par. 65; Niggemeier (2015), par. 51; Schmidt and Sule (2012) p. 369. — Kingreen (2016), par. 22, defends the opposite view by analogy with TFEU, Art. 168(4)(a). This is not convincing: whereas lit. (a) states explicitly that "[the EU's] measures shall not prevent any Member State from maintaining or introducing more stringent protective measures", such a clause is missing in lit. (c). As there is no evidence for it having been overlooked by the Union legislator, it must be assumed, *argumentum e contrario*, that a Member State's right to adopt stricter standards should be excluded for lit. (c).

[30] TFEU, Art. 4(2)(a).

[31] TFEU, Art. 114(1).

[32] Lurger (2018) par. 52; Faltus (2016), p. 600; Kingreen (2016), par. 22; Niggemeier (2015) par. 46.

code relating to medicinal products for human use,[33] the EMA Regulation,[34] the ATMP Regulation[35] and the Clinical Trials Directive,[36] which will soon be replaced by the Clinical Trials Regulation.[37] The field of genetic technology is mainly regulated by the Deliberate Release Directive[38] and the Contained Use Directive.[39]

EU regulations are directly applicable in all Member States;[40] they do not require to be implemented into national law and can establish rights and obligations for all legal subjects in the Member States.[41] In fact, an EU regulation is comparable to a national act of parliament but takes precedence over the latter.[42] On the contrary, EU

[33] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67). A consolidated version of 26.07.2019 is available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0083-20190726&qid=1613345686360&from=EN (accessed 25 Feb 2021).

[34] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1). A consolidated version of 30.03.2019 is available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02004R0726-20190330&qid=1613345878480&from=EN (accessed 25 Feb 2021).

[35] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121). A consolidated version of 26.07.2019 is available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02007R1394-20190726&qid=1613345959831&from=EN (accessed 25 Feb 2021).

[36] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.6.2001, p. 34). A consolidated version of 07.08.2009 is available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0020-20090807&qid=1613346052970&from=EN (accessed 25 Feb 2021).

[37] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L 158, 27.5.2014, p. 1). A consolidated version of 27.05.2014 is available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02014R0536-20140527&qid=1613346140633&from=EN (accessed 25 Feb 2021).

[38] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17.4.2001, p. 1). A consolidated version of 26.07.2019 is available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0018-20190726&qid=1613346223811&from=EN (accessed 25 Feb 2021).

[39] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (OJ L 125, 21.5.2009, p. 75), available at https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32009L0041&qid=1613346290811&from=EN (accessed 25 Feb 2021).

[40] TFEU, Art. 288[2].

[41] European Court of Justice (ECJ), Judgement of 14 December 1971, *Politi*, C-43/71, EU:C:1971:122, par. 9.

[42] ECJ, Judgement of 15 July 1964, *Costa v E.N.E.L.*, C-6/64, EU:C:1964:66.

directives are addressed to the Member States.[43] They require an act of implementation into national law to become effective, most commonly an act of parliament.[44] Germany has implemented the Directive on the Community code relating to medicinal products for human use into the Medicinal Products Act[45] and the Deliberate Release Directive as well as the Directive on the contained use of genetically modified micro-organisms into the Genetic Engineering Act.[46]

By default, it is incumbent upon the Member States to execute and enforce EU law.[47] However, the EU's pharmaceutical legislation is also executed by the European Commission[48] and the European Medicines Agency (EMA).[49] In the field of ATMPs, two committees of the EMA, which are both composed of representatives of the Member States,[50] play an important role: the Committee for Medicinal Products for Human Use (CHMP)[51] and the Committee for Advanced Therapies (CAT).[52]

3.2.3 *Applicability of the EU's Pharmaceutical Legislation*

The scope of the EU's legislation for medicinal products is determined by Art. 2(1) of the Directive on the Community code relating to medicinal products for human use:

> This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.

According to Art. 1 No. 2, the term "medicinal product" encompasses medicinal products by presentation (lit. a) and medicinal products by function (lit. b), i.e. "products the pharmacological properties of which have been scientifically observed and which are genuinely designed to make a medical diagnosis or to restore, correct or modify physiological functions".[53] Genome-edited re-differentiated iPS cells or progenitor cells that are to be transplanted autologously

[43] TFEU, Art. 288[3].

[44] Streinz (2016), par. 485.

[45] Cf. Twelfth Act amending the Medicinal Products Act of 30 July 2004 (Federal Law Gazette Part I p. 2031).

[46] Fenger (2018), § 1 par. 1.

[47] Frenz (2010), pp. 524–525.

[48] Cf. TEU, Art. 17; TFEU, Art. 244–250.

[49] Cf. Regulation (EC) No 726/2004, Art. 55–80.

[50] Regulation (EC) No 726/2004, Art. 61.

[51] Cf. Regulation (EC) No 726/2004, Art. 56(1)(a).

[52] Cf. Regulation (EC) No 726/2004, Art. 56(1)(da); Regulation (EC) 1394/2007, Art. 20–23.

[53] ECJ, Judgement of 15 January 2009, *Hecht-Pharma*, C-140/07, EU:C:2009:5, par. 25; cf. ECJ, Judgement of 15 November 2007, *Commission v Germany*, C-319/05, EU:C:2007:678, par. 61.

for therapeutic purposes in any case fulfil the second category's definition and can therefore be classified as medicinal products.

It might sound tautological that these medicinal products have to be "either prepared industrially or manufactured by a method involving an industrial process".[54] The European Court of Justice draws a clear distinction between the two alternatives, though. According to the Court, the term "prepared industrially" does not refer to the preparation itself but to the manufacturer's aim: it is defined by acting "for profit-making purposes".[55] The nature of the manufacturing process is thus irrelevant.[56]

Following this definition, "manufactured by a method involving an industrial process" appears as a residual clause designed to cover cases in which a medicinal product is manufactured without any profit-making purposes. On this basis—and bearing in mind the principle of *effet utile*[57]—, the "industrial process" must be interpreted as an at least minimally standardised process involving at least a slight degree of mechanisation.[58] In other words: the "industrial process" has to be distinguished from single-unit production.

A scenario in which a combined gene/cell therapy is carried out without any standardisation and mechanisation and without any intention of making a profit is hardly imaginable.

The crucial point is that the medicinal products have to be intended to be placed on the market to fall under EU Law. The "placement on the market" is not defined either. The German legislature interprets this term as "the keeping in stock for sale or for other forms of supply, the exhibiting and offering for sale and the distribution to others":[59] according to this definition, the "placement on the market" encompasses the medicinal product's distribution and the preparatory acts to this aim. Such a conception can be backed by a comparison with legal definitions for the "placement on the market" on similar fields.[60] Nevertheless, this only shifts the problem to the

[54] The German version of the Directive 2001/83/EC tries to resolve the tautology by translating the first alternative (prepared industrially) with *gewerblich hergestellt* (prepared commercially). Nevertheless, as far as the authors could prove, none of the other official language versions has gone this path, what might be the reason for the German version of Regulation (EC) No 1394/2007 returning to *industriell hergestellt* (prepared industrially) in its recital 6 (though Bock (2012a), p. 109 assumes a drafting error or translation error).

[55] ECJ, Judgement of 22 April 2010, *The Queen v Medicines and Healthcare Products Regulatory Agency*, C-62/09, EU:C:2010:219, par. 32.

[56] Bock (2012a), p. 116.

[57] Cf. TFEU, Art. 4(3).

[58] Bock (2012a), p. 126.

[59] Medicinal Products Act, § 4 No. 17.

[60] Cf. Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety (OJ L 031 1.2.2002, p. 1), Art. 3 No. 8: "'placing on the market' means the holding of food or feed for the purpose of sale, including offering for sale or any other form of transfer, whether free of charge or not, and the sale, distribution, and other forms of transfer themselves";

term "distribution": Does "distribution" comprise the medicinal product's application to a patient by the treating physician?

Such an interpretation would take into account the Directive's aim of protecting the patients.[61] Nevertheless, if the term "distribution" covered a medicinal product's application, it would be barely possible to imagine cases in which a medicinal product is not placed on the market as every medicinal product is at least destined to be applied. The "placement on the market" would lose its function as defining the Directive's scope which is a clear sign for an improper interpretation.[62] Therefore, for assuming that a medicinal product is distributed and, thus, placed on the market, it is necessary that the power of disposal over the medicinal product is transferred from one person to another—which is not the case when the medicinal product is applied to the patient.[63]

In consequence, the EU's pharmaceutical legislation applies to combined gene/cell therapies except in the case that the treating physician manufactures the cells himself/herself. Demarcation problems arise in in-house constellations when, in a major hospital, manufacture and application are carried out with divided responsibilities but within the same organisation.[64] In this case and following the general principle that a transfer of the power of disposal is required, as long as the cells always remain under the custody of the same department, it cannot be assumed that

cf. Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed (OJ L 268, 18.10.2003, p. 1), Art. 2 No. 14: "'placing on the market' means the holding of food or feed for the purpose of sale, including offering for sale, or any other form of transfer, whether free of charge or not, and the sale, distribution and other forms of transfer themselves";

cf. Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC (OJ L 309, 24.11.2009, p. 1), Art. 3 No. 9: "'placing on the market' means the holding for the purpose of sale within the Community, including offering for sale or any other form of transfer, whether free of charge or not, and the sale, distribution, and other forms of transfer themselves [. . .]";

cf. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396, 30.12.2006, p. 1), Art. 3 No. 12: "placing on the market: means supplying or making available, whether in return for payment or free of charge, to a third party [. . .]".

[61] Cf. Bock (2012a), p. 99.

[62] Cf. Bock (2012a), p. 102.

[63] Cf. Pfohl (2020), par. 30–33; Krüger (2016), par. 140, 142; Rehmann (2014), § 4 No. 19; Bock (2012a), p. 105; Pabel (1989), p. 760.—The Courts have adopted this definition, cf. inter alia German Federal Court of Justice (BGH), Judgement of 18 September 2013, 2 StR 535/12, NJW 2014:326, par. 14; German Federal Administrative Court (BVerwG), Judgement of 2 December 1993, 3 C 42.01, BVerwGE 93:341, No. 2.2.

[64] Such structures are hardly considered in legal literature; cf. Rehmann (2014), par. 19, who just remarks that division of labour constellations ought to be scrutinised thoroughly.

any distribution takes place as the power of disposal always remains with the department head. On the contrary, if multiple departments are involved, the power of disposal is transferred from one department head to another. The cells are, thus, distributed, and the combined gene/cell therapy therefore falls within the scope of the EU's pharmaceutical legislation.

The ATMP Regulation's scope is identical to the described scope of the Directive on the Community code relating to medicinal products for human use. The European Commission's proposal states it falls "within the global scope of the pharmaceutical legislation",[65] citing explicitly Art. 2(1) of the Directive. The ATMP Regulation is framed as *lex specialis*,[66] its recital 6 also refers to the scope of the Directive on the Community code relating to medicinal products for human use.

The same conclusion can be drawn with reference to the EMA Regulation: Though it is not explicitly labelled as *lex specialis*, the EMA Regulation was issued with the purpose of establishing the procedure for the centralised marketing authorisation envisaged in Art. 6(1) of the Directive on the Community code relating to medicinal products for human use. Therefore, the latter sets out the scope of the EMA Regulation.[67] This is important to bear in mind because it implicates that the exceptions to the marketing authorisation requirements set out in the Directive on the Community code relating to medicinal products for human use also apply to the marketing authorisation granted by the EU in accordance with the provisions of the EMA Regulation.[68]

3.2.4 Classification of Genome-Edited iPS Cells as ATMPs

The EU's legislation on medicinal products distinguishes three types of ATMPs: gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (CTMPs) and tissue engineered products.[69]

Both the tissue engineered products and the CTMPs contain or consist of cells or tissues that have been substantially manipulated: their biological characteristics, physiological functions or structural properties relevant for the intended use have

[65] European Commission (2005), p. 3.

[66] Regulation (EC) No 1394/2007, Art. 1, 2(1), recital 6.

[67] This result is built on various indications: First, the EMA Regulation refers back to the definitions of the Directive 2001/83/EC (Art. 2[1]). Second, the criteria for granting a marketing authorisation under the EMA Regulation are the same as under Directive 2001/83/EC (Art. 6(1), 7(a), recital 14). Third, the marketing authorisation granted by the EU in accordance with the provisions of the EMA Regulation has the same effects as a marketing authorisation granted by the Member States in accordance with the Directive 2001/83/EC (Art. 13(1), recital 6).

[68] See Sect. 3.3.4.3.

[69] Regulation (EC) No 1394/2007, Art. 2(1)(a).

been altered—or they are not intended to be used for the same essential function(s) in the recipient as in the donor.[70]

The difference between these two categories of ATMPs consists in the intended use: the purpose of a tissue engineered product is to regenerate, repair or replace a human tissue whilst a CTMP serves the purpose of treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.[71]

In contrast, GTMPs may, but do not necessarily, contain or consist of cells or tissues. They are characterised by containing an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence. The medicinal product's therapeutic, prophylactic or diagnostic effect has to relate directly to the recombinant nucleic acid sequence it contains or to the product of genetic expression of this sequence.[72]

Genome-edited iPS cells are cells that have been substantially manipulated through reprogramming, genome editing and re-differentiation.[73] In the case of a combined gene/cell therapy, the cells are used for the cure of hereditable diseases. Therefore, they fulfil the definition of a CTMP. As their therapeutic effect arises from the genetic expression of the recombinant nucleic acid (i.e. the genome edited DNA sequence), they can also be classified as GTMPs.[74] According to the classification rules,[75] they are therefore regulated as GTMPs.

3.2.5 Classification of Genome-Edited iPS Cells as GMOs

The EU's regulatory approach in the field of genetic technology departs from the definition of genetically modified organisms (GMOs), which delimits the scope of both the Deliberate Release Directive[76] and the Contained Use Directive.[77]

[70] Regulation (EC) No 1394/2007, Art. 2(1)(c).—Annex I to Regulation (EC) No 1394/2007 contains a negative list of manipulations that are not considered as substantial (cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation and vitrification).

[71] Cf. the definitions for tissue engineered products in Regulation (EC) No 1394/2007, Art. 2(1)(b), and for CTMPs in Regulation (EC) No 1394/2007, Annex I, Part IV, par. 2.2.

[72] Cf. Regulation (EC) No 1394/2007, Annex I, Part IV, par. 2.1.

[73] Cf. Faltus (2016), p. 698, for iPS cells.

[74] Cf. Anliker et al. (2015), p. 1274.

[75] Regulation (EC) No 1394/2007, Art. 2(4) and (5).

[76] Cf. Directive 2001/17/EC, Art. 1.

[77] Cf. Directive 2009/41/EC, Art. 1. Admittedly, Directive 2009/41/EC applies to genetically modified micro-organisms (GMMs) only. However, this Directive on the contained use of GMMs has been implemented by most EU Member States in such a way that the respective national rules extend to all GMOs.

Accordingly, the German Genetic Engineering Act, which implements both directives into national law, also requires a GMO for its applicability.[78]

GMOs are organisms "in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination".[79] An organism is "any biological entity capable of replication or of transferring genetic material".[80] Genome-edited iPS cells are biological entities and, in principle, capable of replication. They are, thus, organisms.[81] The artificial alteration itself is not defined; there are only lists for techniques that result[82] or do not result[83] in artificial genetic modifications. Furthermore, some techniques—one of them mutagenesis—are explicitly excluded from the scope, which implies that they would fulfil the definition of an artificial alteration.[84]

In a broadly discussed judgement, the European Court of Justice held that the ambiguous definition had to be interpreted in such a way that the use of any non-natural procedure necessarily resulted in an artificial genetic modification[85]—notwithstanding the fact that the alteration itself (i.e. the result) might not be distinguishable from (natural) alterations resulting from natural processes or from techniques excluded from the scope of EU legislation on GMOs, i.e. from mutagenesis.[86] Hence, alterations resulting from genome editing techniques, e.g. CRISPR-Cas, are artificial genetic modifications.[87] Furthermore, they are not excluded from the scope of the Deliberate Release Directive as they are not "obtained by means of techniques/methods which have conventionally been used in a number of applications and have a long safety record".[88] Though the ECJ judgement directly interprets only the Deliberate Release Directive, its conclusions seem to be equally applicable to the Contained Use Directive[89] and thus cover the entire EU legislation on GMOs.

[78] Genetic Engineering Act, § 2(1).

[79] Directive 2001/18/EC, Art. 2(2); cf. Directive 2009/41/EC, Art. 2(b); Genetic Engineering Act, § 3 No. 3.

[80] Directive 2001/18/EC, Art. 2(1); cf. Directive 2009/41/EC, Art. 2(a); Genetic Engineering Act, § 3 No. 1.

[81] Cf. Directive 2009/41/EC, Art. 2(a), which explicitly names "cells in culture".

[82] Directive 2001/18/EC, Annex I A, part 1; Directive 2009/41/EC, Annex I, part A; cf. Genetic Engineering Act, § 3 No. 3a. These are non-exhaustive lists.

[83] Directive 2001/18/EC, Annex I A, part 2; Directive 2009/41/EC, Annex I, part B; cf. Genetic Engineering Act, § 3 No. 3b. These are exhaustive lists.

[84] Directive 2001/18/EC, Art. 3(1), Annex I B; cf. Directive 2009/41/EC, Art. 3(1)(a), Annex II, part A; Genetic Engineering Act, § 3 No. 3b.

[85] ECJ, Judgement of 25 July 2018, *Confédération paysanne* et al., C-538/16, EU:C:2018:583, par. 29 et seq.

[86] Cf. Leopoldina et al. (2019), p. 31.

[87] ECJ, Judgement of 25 July 2018, *Confédération paysanne* et al., C-538/16, EU:C:2018:583, par. 30.

[88] ECJ, Judgement of 25 July 2018, *Confédération paysanne* et al., C-538/16, EU:C:2018:583, par. 51.

[89] Voigt (2020), p. 61; Spranger (2019), p. 12; Kahrmann and Leggewie (2018), p. 764.

In conclusion, genome-edited iPS cells are to be considered GMOs.[90] However, as human beings are explicitly excluded from the definition of GMOs,[91] the cells lose this status the moment they are administered to the patient.[92]

3.3 Regulatory Prerequisites for Combined Gene/Cell Therapy Using Genome-Edited Human iPS Cells to Be Differentiated into Somatic Cells for Autologous Re-Transplantation

In case of a combined gene/cell therapy, various steps can be distinguished. The treatment begins with the biopsy of the cells. These are then processed. For example, somatic cells (e.g. from skin or liver) are first reprogrammed into induced pluripotent stem cells (iPS cells). The resulting iPS cells are then genome-edited via, e.g., CRISPR-Cas and finally re-differentiated into somatic cells (or progenitor cells). If the processing has not been carried out by the treating physician, the latter must obtain the resulting cells from the manufacturer. Finally, the cells are administered to the patient.

The legal system of the EU uses preventive bans with an authorisation option—a concept common in policing law[93]—in order to ensure the safety of such a combined gene/cell therapy. Several stages of the treatment are subject to such preliminary bans: the biopsy or donation of the cells requires an authorisation (see Sect. 3.3.1) as well as the processing of the cells (see Sect. 3.3.2) and the placement on the market (see Sect. 3.3.3). Besides, under certain circumstances, EU law allows the administration of medicinal products without marketing authorisation (see Sect. 3.3.4).

3.3.1 Cell Procurement

By default, "donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells"[94] are governed by the Tissue Directive.[95]

[90] Cf. Dederer and Frenken (2021), p. 5.

[91] Directive 2001/18/EC, Art. 2(2); cf. Directive 2009/41/EC, Art. 2(b); Genetic Engineering Act, § 3 No. 3.

[92] Dederer and Herdegen (2020), par. 95.

[93] Cf. Gromitsaris (1997), p. 402; Preusche (1980), p. 49.

[94] Directive 2004/23/EC, Art. 2(1)[1].

[95] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 102, 7.4.2004, p. 48). A consolidated

However, if the tissues or cells fall under specific legislation—as it is the case with genome-edited human iPS cells for combined gene/cell therapy—the Tissue Directive applies to donation, procurement and testing only.[96]

Furthermore, "tissues and cells used as an autologous graft within the same surgical procedure" are excluded from the Tissue Directive's scope.[97] However, this exception does not apply even in the case that the treating physician removes and manufactures the cells himself/herself: as the cells are reprogrammed, genome-edited and differentiated before being (autologously) re-transplanted, the biopsy cannot be considered to take place "within the same surgical procedure" as the re-transplantation.[98] Consequently, the Tissue Directive applies to the biopsy (and testing) of cells for combined gene/cell therapy in any constellation.

It obliges the Member States to establish an authorisation requirement for procurement and testing of cells. By this means, the Member States shall ensure the observance of the principles of good practice which mainly consist in a documentation-based quality system.[99] Moreover, the authorisation requirement guarantees the qualification of the (medical) staff[100] and suitability of the premises.[101] Although the European Commission is empowered to specify the technical requirements,[102] the principles of good practice are mainly determined by the Member States' medical societies.[103] Hence, they vary considerably from one Member State to another. They may be, notably in the case of Germany, even non-uniform within one Member State, and they tend to set lower standards than the principles and guidelines of GMP.[104]

Germany has incorporated the requirement of an authorisation for cell procurement *(Erlaubnis für die Gewinnung von Gewebe)* into the Medicinal Products

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version of 07.08.2009 is available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02004L0023-20090807&qid=1613851286698&from=DE (accessed 25 Feb 2021).

[96] Directive 2004/23/EC, Art. 2(1)[2]; Regulation (EC) No 1394/2004, Art. 3.

[97] Directive 2004/23/EC, Art. 2(2)(a); cf. Medicinal Products Act, § 4a No. 3.

[98] Cf. Faltus (2016), pp. 631–635.

[99] Cf. Directive 2004/23/EC, Art. 16(1).

[100] Directive 2004/23/EC, Art. 5(1), cf. Art. 17, 18.

[101] Directive 2004/23/EC, Art. 5(2).

[102] Directive 2004/23/EC, Art. 28, 29.—Based on these provisions, the European Commission has adopted various implementing acts. Of particular relevance is the Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells (OJ L 38, 9.2.2006, p. 40). A consolidated version of 17.12.2018 is available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006L0017-20121217&qid=1613948054572&from=EN (accessed 25 Feb 2021).

[103] See Guidelines of the German Society of Surgery (DGCH) on Good Professional Practice (GPP) on the Removal of Human Tissues and Cells for Manufacturing a Medicinal Product (*Leitfaden der Deutschen Gesellschaft für Chirurgie zur Guten Fachlichen Praxis (GFP) für die Entnahme von menschlichen Geweben und Zellen zur Herstellung eines Arzneimittels*). Regrettably, there is no English translation available.

[104] Cf. Faltus (2016), pp. 677–678.—For the GMP standards see Sect. 3.3.2.

Act.[105] If the applicant disposes of qualified staff[106] as well as suitable premises[107] and it is guaranteed that the procurement is carried out in accordance with the principles of good practice,[108] the authorisation is granted by the authorities established for the execution of the Medicinal Products Act by the *Länder*.[109]

Nevertheless, in the case that the treating physician manufactures the cells himself/herself, he/she must comply with principles and guidelines of GMP.[110] In this case, the authorisation for cell procurement is granted under the provisions for the manufacturing authorisation *(Herstellungserlaubnis)*.[111] In practice, both the cell procurement and the manufacturing can be covered by a single authorisation.[112]

3.3.2 Manufacture

The Directive on the Community code relating to medicinal products for human use obliges the Member States to establish an authorisation requirement for the manufacture of medicinal products within their territory.[113] As the aim of this provision is to safeguard public health,[114] any form of manufacturing is covered.[115]

The applicant for a manufacturing authorisation has to specify the medicinal products and pharmaceutical forms which are to be manufactured and the place where they are to be manufactured.[116] He/she is required to have suitable and sufficient premises, technical equipment and control facilities at his/her disposal.[117] At least one qualified person has to be responsible that every batch of medicinal products has been manufactured, checked and packed in compliance with the law.[118] This person generally must have completed university studies of at least 4 years in pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and

[105] Medicinal Products Act, § 20b.

[106] Medicinal Products Act, § 20b(1) No. 1, 2.

[107] Medicinal Products Act, § 20b(1) No. 3.

[108] Medicinal Products Act, § 20b(1) No. 4.

[109] Medicinal Products Act, § 20b(1).

[110] Faltus (2016), p. 638.—This is the result of an exception to § 20b of the Medicinal Products Act (established in Medicinal Products Act, § 20d). § 20b of the Medicinal Products Act is inapplicable. Therefore, § 13 of the Medicinal Products Act becomes applicable.

[111] See Sect. 3.3.2.

[112] Renner et al. (2016), p. 92.

[113] Directive 2001/83/EC, Art. 40(1).

[114] Directive 2001/83/EC, recital 2; cf. recital 35.

[115] Faltus (2016), p. 657, reaches the same conclusion (but referring to the incorporation of the manufacturing authorisation requirement into the Medicinal Product Act); cf. Kügel (2016b), par. 4.

[116] Directive 2001/83/EC, Art. 41(a); cf. Medicinal Products Act, § 16.

[117] Directive 2001/83/EC, Art. 41(b); cf. Medicinal Products Act, § 14(1) No. 6.

[118] Directive 2001/83/EC, Art. 41(c), 48, 51; cf. Medicinal Products Act, § 14(1) No. 1.

technology or biology, and must have acquired practical experience over at least 2 years.[119]

The authorisation shall be granted within a period of 90 days[120] if an inquiry has proven the accuracy of the particulars furnished by the applicant.[121] It only applies to the premises, the medicinal products and the pharmaceutical forms specified in the application.[122] In any case, the authority has to give reasons for its decision.[123]

Any manufacturer of medicinal products within the EU has to comply with the principles and guidelines of good manufacturing practice for medicinal products (GMP).[124] The European Commission is entitled to specify these principles and guidelines.[125] It has exercised this power by adopting, inter alia, directives in 2003[126] and 2017,[127] regulations in 2014[128] and 2017[129] as well as comprehensive guidelines.[130]

[119] Directive 2001/83/EC, Art. 49(1), (2), (3); Medicinal Products Act, § 15.—There are some exceptions to these requirements for the personal qualifications; Directive 2001/83/EC, Art. 49(2) and (3) lists other forms of theoretical and practical education which are regarded as equivalent.

[120] Directive 2001/83/EC, Art. 43, cf. Medicinal Products Act, § 17.

[121] Directive 2001/83/EC, Art. 42(1); cf. Medicinal Products Act, § 64(3a).

[122] Directive 2001/83/EC, Art. 42(3); cf. Medicinal Products Act, § 16.

[123] Directive 2001/83/EC, Art. 125[1].

[124] Directive 2001/83/EC, Art. 46(f); cf. Medicinal Products Act, § 14(1) No. 6a in conjunction with Ordinance on Manufacture of Medicinal Products and Active Substances, § 3(1), (2).

[125] Directive 2001/83/EC, Art. 47[1].

[126] Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (OJ L 262, 14.10.2003, p. 22), available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003L0094&qid=1614032711809&from=EN (accessed 25 Feb 2021).

[127] Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use (OJ L 238, 16.9.2017, p. 44), available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017L1572&from=EN (accessed 25 Feb 2021).

[128] Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use (OJ L 337, 25.11.2014, p. 1), available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R1252&from=EN (accessed 25 Feb 2021).

[129] Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections (OJ L 238, 16.9.2017, p. 12), available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R1569&from=EN (accessed 25 Feb 2021).

[130] An overview of the guidelines on good manufacturing practice is available at https://ec.europa.eu/health/documents/eudralex/vol-4_en (accessed 25 Feb 2021).

Germany has incorporated the authorisation requirement for the manufacture of medicinal products *(Herstellungserlaubnis)* into Chapter 3 of the Medicinal Products Act.[131] The authorities established for the execution of the Medicinal Products Act by the *Länder* are competent for granting the authorisation for the manufacturing facilities situated on the territory of the respective *Land*.[132] They shall reach their decision in consultation with the PEI,[133] which means that the PEI must be given the opportunity to submit a non-binding opinion. The authority of the respective *Land* must consider the opinion when taking its decision but is allowed to deviate from the opinion based on an appropriate justification.[134] The principles and guidelines of GMP have been incorporated into the Ordinance on Manufacture of Medicinal Products and Active Substances.[135]

Beyond the direct scope of the Directive on the Community code relating to medicinal products for human use—i.e. medicinal products which have obtained a marketing authorisation[136]—, an authorisation is also required for the manufacture of medicinal products for clinical trials,[137] of medicinal products falling under the hospital exemption[138] and even of medicinal products that are manufactured by the treating physician himself/herself.[139] Thus, any medicinal product administered to a patient in Germany must be manufactured in compliance with the principles and guidelines of GMP.

3.3.3 Placement on the Market

Within the EU, any medicinal product that is to be placed on the market of a Member State requires a marketing authorisation.[140] By default, the authorisation is granted by one Member State.[141] Once a medicinal product has obtained a marketing authorisation, the holder can apply for the recognition of this authorisation in one

[131] Medicinal Products Act, § 13(1).

[132] Medicinal Products Act, § 13(4).

[133] Medicinal Products Act, § 13(4) in conjunction with § 77 (1) and (2).

[134] Cf. Weber K (2019), entry "Einvernehmen".

[135] Ordinance on Manufacture of Medicinal Products and Active Substances *(Arzneimittel- und Wirkstoffherstellungsverordnung)* of 3 November 2006 (Federal Law Gazette Part I p. 2523), last amended by Article 3 of the Ordinance of 2 July 2018 (Federal Law Gazette I p. 1080). Regrettably, there is no English translation available.

[136] See Sect. 3.3.3.1.

[137] See Sect. 3.3.3.3.

[138] See Sect. 3.3.4.2.

[139] See Sect. 3.3.4.4.

[140] Directive 2001/83/EC, Art. 6(1); Medicinal Products Act, § 21.

[141] Directive 2001/83/EC, Art. 8(1), 28(2); cf. Medicinal Products Act, §§ 21, 22.

or more other Member State(s).[142] Alternatively, it is possible to apply directly for a marketing authorisation in more than one Member State. In this case, the procedure is conducted by one Member States, the so-called 'reference Member State', under participation of the others.[143]

However, for some medicinal products, the EMA Regulation imposes a centralised procedure, inter alia for ATMPs. These medicinal products are subject to a marketing authorisation granted by the EU.[144]

3.3.3.1 Centralised Marketing Authorisation

The application for a marketing authorisation is to be submitted to the EMA.[145] It has to include the particulars and documents as referred to in Art. 8(3) and 11 of, and Annex I to, Directive 2001/83/EC.[146] These particulars and documents include an evaluation of the potential environmental risks posed by the medicinal product,[147] the results of pharmaceutical (physico-chemical, biological or microbiological) tests, pre-clinical (toxicological and pharmacological) tests and clinical trials[148] as well as a proof of the applicant's manufacturing authorisation.[149] Moreover, the application has to be accompanied by an environmental risk assessment in accordance with the Deliberate Release Directive[150] as genome-edited iPS cells are subject to the legislation on GMOs.[151]

Within EMA, the CAT is responsible for drawing up EMA's opinion on whether the application is admissible and the medicinal product can be approved.[152] For the evaluation of the environmental risk assessment, it consults the bodies competent for the enforcement of the Deliberate Release Directive.[153] The draft is finally approved by the CHMP within 210 days from the submission of the application.[154] This time limit can be suspended if the CHMP asks the applicant for supplementary informa-

[142] Directive 2001/83/EC, Art. 28(2); cf. Medicinal Products Act, § 25b(2).
[143] Directive 2001/83/EC, Art. 28(1), (3); cf. Medicinal Products Act, § 25b(1), (3).
[144] Regulation (EC) No 726/2004, Art. 3(1) in conjunction with Annex I No. 1a.
[145] Regulation (EC) No 726/2004, Art. 4(1).
[146] Regulation (EC) No 726/2004, Art. 6(1).
[147] Directive 2001/83/EC, Art. 8(3)(ca).
[148] Directive 2001/83/EC, Art. 8(3)(i); see Sect. 3.3.3.3.
[149] Directive 2001/83/EC, Art. 8(3)(k).
[150] Regulation (EC) No 726/2004, Art. 6(2)(a)-(c).
[151] See Sect. 3.2.5.
[152] Regulation (EC) No 1394/2007, Art. 23(a).
[153] Regulation (EC) No 726/2004, Art. 6(3)[4].
[154] Regulation (EC) No 726/2004, Art. 5(2), 6(3)[1]; Regulation (EC) No 1394/2007, Art. 23(a).

tion and explanations until the latter has supplied the requested data.[155] However, the scientific analysis of the application regularly shall take at least 80 days.[156]

In its assessment of the application, the EMA evaluates quality, safety and efficacy of the medicinal product. Its scientific standards are laid down in numerous guidelines.[157] For combined gene/cell therapy, the guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products[158] and the guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells[159] are of particular relevance. In addition, the guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to ATMPs provides an insight into the EMA's view on ATMPs.[160] Finally, the aspects concerning the environmental risk assessment for GMOs are discussed in the guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products.[161]

If the result of the evaluation is negative, the EMA forthwith informs the applicant.[162] The applicant has the possibility of requesting a re-examination of EMA's opinion within 15 days. The detailed grounds for the request must be submitted within 60 days. In this case, the CHMP re-examines its opinion within another 60 days.[163]

Regardless of the result, the Agency sends the final opinion to the European Commission, to all Member States and to the applicant within 15 days after its

[155] Regulation (EC) No 726/2004, Art. 7(c).

[156] Regulation (EC) No 726/2004, Art. 6(3)[2].

[157] An overview of the guidelines relevant for ATMPs in general and GTMPs in particular is available at https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products and at https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-gene-therapy (both accessed 25 Feb 2021).

[158] EMA, Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products, 22 March 2018, EMA/CAT/80183/2014, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-gene-therapy-medicinal-products_en.pdf (accessed 25 Feb 2021).

[159] EMA, Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells, 13 April 2012, EMA/CAT/GTWP/671639/2008, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically-modified_en.pdf (accessed 25 Feb 2021).

[160] EMA, Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products, 11 February 2013, EMA/CAT/CPWP/686637/2011, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-based-approach-according-annex-i-part-iv-directive-2001/83/ec-applied-advanced-therapy-medicinal-products_en.pdf (accessed 25 Feb 2021).

[161] EMA, Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products, 30 May 2008, EMEA/CHMP/GTWP/125491/2006, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-requirements-environmental-risk-assessment-gene-therapy-medicinal-products_en.pdf (accessed 25 Feb 2021).

[162] Regulation (EC) No 726/2004, Art. 9(1).

[163] Regulation (EC) No 726/2004, Art. 9(2).

adoption.[164] Within another 15 days, the European Commission drafts its decision and forwards the draft to the Member States and the applicant.[165] The European Commission is not bound by EMA's opinion. However, a detailed explanation is required if the draft decision differs from EMA's opinion.[166] If a Member State's written observations raise important new questions, the procedure can be suspended. In this case, the application is referred back to the EMA.[167] Otherwise, the draft of the European Commission's decision is put to the vote of the Standing Committee on Medicinal Products for Human Use, composed by representatives of the Member States.[168] This procedure regularly takes at least 14 days.[169] After the Standing Committee has delivered a positive opinion, the European Commission takes the final decision within 15 days.[170] The decision states in detail the reasons on which it is based.[171]

The marketing authorisation granted under the centralised procedure is valid for 5 years throughout the EU.[172] After this period, the authorisation can be renewed on the basis of a re-evaluation of the risk-benefit balance[173] and is then regularly valid without any temporal limit.[174]

3.3.3.2 Special Programmes

Beyond the regular (centralised) procedure for obtaining a marketing authorisation, the EU has developed various schemes in order to foster innovation and to guarantee the availability of medicinal products required for public health. Four programmes shall be described below. If the respective prerequisites are met, they can also be combined.[175]

First, based on its general mandate to provide scientific advice "on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy

[164] Regulation (EC) No 726/2004, Art. 9(3).

[165] Regulation (EC) No 726/2004, Art. 10(1)[1], [5].

[166] Regulation (EC) No 726/2004, Art. 10(1)[4].

[167] Regulation (EC) No 726/2004, Art. 10(4).

[168] Regulation (EC) No 726/2004, Art. 10(2), 87(1), (3); Regulation (EU) No 182/2011, Art. 3, 5, 10, 11, 13(1)(b), (e).

[169] Cf. Regulation (EU) No 182/2011, Art. 3(3).

[170] Regulation (EC) No 726/2004, Art. 10(2), 87(3); Regulation (EU) No 182/2011, Art. 13(1)(b), 5(2).—Since 2013, the Standing Committee on Medicinal Products for Human Use has given a positive opinion on all drafts submitted by the European Commission (cf. the annual reports from the Commission on the working of the comitology committees available at https://ec.europa.eu/transparency/regcomitology/index.cfm?do=Report.Report, accessed 25 Feb 2021).

[171] Regulation (EC) No 726/2004, Art. 81(1).

[172] Regulation (EC) No 726/2004, Art. 14(1), 13(1).

[173] Regulation (EC) No 726/2004, Art. 14(2).

[174] Regulation (EC) No 726/2004, Art. 14(3).

[175] Cf. Dederer and Frenken (2021), pp. 33–35.

of medicinal products",[176] the EMA has launched the so-called PRIME scheme[177] designed for medicinal products that demonstrate the potential to address an unmet medical need.[178] Drug developers can apply for PRIME as soon as first promising clinical evidence is available, academic investigators and micro-, small- and medium-sized enterprises even earlier.[179] Its main features are the early appointment of the rapporteurs of both CHMP and CAT, which will then provide scientific advice until the submission of an application for marketing authorisation, beginning with a kick-off meeting in which all the relevant experts are present.[180]

Second, in emergency situations, the EMA allows for a rolling review. Within the EU, this instrument is not codified but used as an *ad hoc* procedure. In several review cycles, the CHMP and the CAT assess the data for a "highly promising application" as soon as they become available for a period of 2 weeks. The applicant is given feedback in form of a list of questions which can be answered in the course of the subsequent submissions. He/she is informed when CHMP and CAT consider the evaluated data to be sufficient for a successful application for marketing authorisation, which he/she then is expected to submit.[181] In the current COVID-19 pandemic, the data for the marketing authorisations of, inter alia, the vaccines of AstraZeneca in collaboration with the University of Oxford,[182] of BioNTech in collaboration with Pfizer[183] and of CureVac[184] have been, or are being, evaluated in a rolling review.

Third, applicants can request an accelerated assessment procedure for medicinal products that "are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation".[185] In this case, the CHMP draws up EMA's opinion within 150 days (instead of 210 days).[186]

[176] Regulation (EC) No 726/2004, Art. 57(1)[2](n).

[177] PRIME is an acronym for priority medicines.

[178] EMA, European Medicines Agency Guidance for applicants seeking access to PRIME scheme, 7 May 2018, EMA/191104/2015, available at https://www.ema.europa.eu/en/documents/other/european-medicines-agency-guidance-applicants-seeking-access-prime-scheme_en.pdf (accessed 25 Feb 2021), p. 4.

[179] Ibid., p. 4.

[180] Ibid., p. 6–8.

[181] EMA (2020a), pp. 3–4.

[182] EMA (2020c).

[183] EMA (2020d).

[184] EMA (2021c).

[185] Regulation (EC) No 2004/726, Art. 14(9)[1]; see EMA, Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004, 25 February 2016, EMA/CHMP/671361/2015 Rev. 1, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-procedure-accelerated/2004_en.pdf (accessed 25 Feb 2021).

[186] Regulation (EC) No 2004/726, Art. 14(9)[2].

Fourth, medicinal products can be granted a conditional marketing authorisation based on preliminary evidence, i.e. prior to the submission of comprehensive clinical or—in emergency situations—even pre-clinical or pharmaceutical data.[187] This regulatory pathway is offered to medicinal products for the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases that address an unmet medical need.[188] A conditional marketing authorisation can be granted if the risk-benefit balance of the medicinal product is favourable and the applicant is likely to be able to provide comprehensive data.[189] It is valid for 1 year throughout the EU; afterwards, it can be renewed.[190] The applicant is obliged to gain further evidence for the medicinal product's quality, safety and efficacy.[191] On this basis, the holder of the conditional marketing authorisation may apply for a regular marketing authorisation.[192] In the current COVID-19 pandemic, the vaccines of AstraZeneca in collaboration with the University of Oxford[193] and of BioNTech in collaboration with Pfizer,[194] inter alia, have received a conditional marketing authorisation. However, the possibility of a conditional marketing authorisation faces criticism for transferring risks from drug developers to patients and healthcare systems in general.[195]

3.3.3.3 Clinical Trials

For the regular marketing authorisation as well as for a conditional marketing authorisation, clinical trials are required in order to demonstrate quality, safety and

[187] Regulation (EC) No 2004/726, Art. 14-1(1); see EMA, Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004, 25 February 2016, EMA/CHMP/509951/2006, Rev.1, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-commission-regulation-ec/2006-conditional-marketing-authorisation-medicinal-products-human-use-falling_en.pdf (accessed 25 Feb 2021).

[188] Regulation (EC) No 2004/726, Art. 14-1(1). — The unmet medical need is defined as "a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected" (Regulation (EC) No 2004/726, Art. 14-1(2)).

[189] Regulation (EC) No 2004/726, Art. 14-1(3).

[190] Regulation (EC) No 2004/726, Art. 14-1(7).

[191] Regulation (EC) No 2004/726, Art. 14-1(4), (5).

[192] Regulation (EC) No 2004/726, Art. 14-1(8).

[193] EMA (2021b).

[194] EMA (2020b).

[195] EASAC, FEAM (2020), p. 10; see Banzi et al. (2017); MacPherson and Kimmelman (2019).

efficacy of a medicinal product. Within the EU, clinical trials of all phases are subject to the principles of good clinical practice (GCP),[196] which were adopted by the European Commission.[197] The Member States are competent for their enforcement.[198] Germany has incorporated the Clinical Trials Directive into Chapter VI of the Medicinal Products Act and into the GCP Ordinance.[199]

Clinical trials of ATMPs may only be commenced after a double evaluation. The sponsor, i.e. the natural or legal person responsible for initiation and management of the clinical trial as well as for its funding,[200] requires both a written[201] authorisation of the competent authority—in Germany: the PEI[202]—based on a scientific evaluation and a favourable opinion of an ethics committee based on an ethical evaluation.[203] The two procedures may take place simultaneously or one after the other.[204]

In addition,[205] the deliberate release of any GMO within the EU, i.e. its intentional introduction into the environment without specific containment measures,[206] has to be notified to and authorised by the competent authority.[207] In Germany, this would be the Federal Office of Consumer Protection and Food Safety.[208] However, unlike most Member States,[209] Germany has opted for a single administrative procedure ("one door, one key") for the authorisation of clinical trials of ATMPs containing or consisting of GMOs. The PEI's authorisation is granted in consultation with the Federal Office of Consumer Protection and Food Safety,[210] i.e. the latter

[196] Directive 2001/20/EC, Art. 1(4), recital 15; Medicinal Products Act, § 40(1).

[197] Based on Directive 2001/20/EC, Art. 1(3), the European Commission has issued the Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (OJ L 91, 9.4.2005, p. 13), available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32005L0028&qid=1627475770435&from=EN (accessed 25 Feb 2021).

[198] Directive 2001/20/EC, Art. 9(1).

[199] GCP Ordinance *(GCP-Verordnung)* in the version published on 9 August 2004 (Federal Law Gazette Part I p. 2081), last amended by Article 8 of the Act of 19 October 2012 (Federal Law Gazette I p. 2192). Regrettably, there is no English translation available.

[200] Directive 2001/20/EC, Art. 2(e); Medicinal Products Act. § 4(24).

[201] Directive 2001/20/EC, Art. 9(6); Medicinal Products Act, § 42(2).

[202] Medicinal Products Act, § 40(1) in conjunction with § 77 (1) and (2).

[203] Directive 2001/20/EC, Art. 9(1); Medicinal Products Act, § 40(1).

[204] Directive 2001/20/EC, Art. 9(1).

[205] Cf. Directive 2001/20/EC, Art. 9(7).

[206] Directive 2001/18/EC, Art. 2(3); Genetic Engineering Act, § 3 No. 5.

[207] Directive 2001/18/EC, Art. 6(1), (8); Genetic Engineering Act, § 14(1) No. 1.

[208] Genetic Engineering Act, §§ 14(1) No. 1, 31.

[209] For an overview on the incorporation of EU legislation on GMO into the Member States' domestic law with regard to investigational medicinal products, cf. https://ec.europa.eu/health/human-use/advanced-therapies/gmo_investiganional_de (accessed 25 Feb 2021). Only Estonia, Greece, Lithuania and Sweden have adopted a similar approach to Germany.

[210] GCP Ordinance, § 9(4); cf. Genetic Engineering Act, §§ 14(1), 31.

must be given the opportunity to submit a non-binding statement.[211] Hence, the pharmaceutical authorisation encompasses the deliberate release authorisation.[212]

The procedure for obtaining an authorisation is initiated by an application of the sponsor.[213] A guidance of the European Commission details the application's format and contents.[214] The European Commission also provides a form for the application on its website.[215] Among the documentation to be submitted are detailed information on objective and design of the trials as well as on their endpoints,[216] the protocol,[217] the results of pre-clinical trials,[218] an environmental risk assessment[219] and the manufacturing authorisation[220] or importation authorisation if the product is manufactured in a country outside the EU.[221] Hence, the investigational medicinal product has to be manufactured in accordance with the principles and guidelines of good manufacturing practice for medicinal products for human use (GMP).[222]

Within 10 days, the PEI confirms the receipt of a valid application. If the documents submitted are incomplete, the sponsor is set a time-limit of 14 days for their supplementation.[223] The application is examined for a maximum period of 90 days, which can be extended to a maximum period of 180 days if the PEI decides to consult experts or to request expert opinions.[224] After the evaluation, the clinical trial is either authorised or the sponsor is notified the grounds for non-acceptance. In this case, the sponsor is set a period of 90 days for amending the content of the application. If the sponsor amends the request accordingly, the PEI decides on the application within a period of 30 days.[225]

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[211] Cf. Weber K (2019), entry "Einvernehmen".

[212] GCP Ordinance, § 9(4).

[213] Directive 2001/20/EC, Art. 9(2); Medicinal Products Act, § 42(2).

[214] European Commission, Communication from the Commission—Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) (2010/C 82/01), available at https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:en:PDF (accessed 25 Feb 2021); which is based on Directive 2001/20/EC, Art. 9(8). The GCP Ordinance lists the information and documents that must accompany the application in § 7(2), (3) and (4).

[215] Annex 1 to CT-1: Clinical trial Application Form, available at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/application-form_en.pdf (accessed 25 Feb 2021).

[216] GCP Ordinance, § 7(2) No. 9.

[217] GCP Ordinance, § 7(2) No. 3.

[218] Medicinal Products Act, § 42(2).

[219] GCP Ordinance, § 7(4) No. 3.

[220] Directive 2001/20/EC, Art. 13(3)(a); GCP Ordinance, § 7(4) No. 1d.

[221] Directive 2001/20/EC, Art. 13(3)(b); GCP Ordinance, § 7(4) No. 1e.

[222] See Sect. 3.3.2; cf. Directive 2001/20/EC, recital 12.

[223] GCP Ordinance, § 9(1).

[224] Directive 2001/20/EC, Art. 9(4); Medicinal Products Act, § 42(2), GCP Ordinance, § 9(4).

[225] Directive 2001/20/EC, Art. 9(3); Medicinal Products Act, § 42(2), GCP Ordinance, § 9(2).

The decision is based on the guidelines of the EMA,[226] in particular on the guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products.[227] Currently, a guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials is available as draft version only.[228] In addition, the guidelines relating to the marketing authorisation of GTMPs can be consulted.[229]

The PEI evaluates, inter alia, pharmacodynamics, pharmacokinetics and potential toxicity of the medicinal product, as well as the dosing.[230] In the assessment of the safety of an ATMP containing or consisting of GMOs, the potential for insertional oncogenesis may be of particular significance. However, "performance of tumorigenicity studies for [GTMPs] will only be expected if indicated by the product construct, for example, if a [GTMP] is expressing a growth factor."[231]

For the evaluation of the environmental risk assessment, the guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products[232] is of special importance. The PEI—in consultation with the Federal Office of Consumer Protection and Food Safety[233]—assesses the risk the medicinal product poses to the environment and in particular to human beings other than the patient who might be exposed to the ATMP. To this aim, potential adverse effects of the medicinal product are identified, and the likelihood of release or transmission is determined. On this basis, the PEI establishes the measures that have to be implemented in order to reduce the risk posed by the medicinal product.[234]

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[226] An overview of the guidelines relevant for ATMPs in general and GTMPs in particular is available at https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products and at https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-gene-therapy (both accessed 25 Feb 2021).

[227] EMA, Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products, 30 May 2008, EMEA/CHMP/GTWP/125459/2006, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-studies-required-first-clinical-use-gene-therapy-medicinal-products_en.pdf (accessed 25 Feb 2021).

[228] EMA, Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials, Draft, 31 January 2019, EMA/CAT/852602/2018, available at https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy_en.pdf (accessed 25 Feb 2021).

[229] See Sect. 3.3.3.1.

[230] Renner et al. (2016), p. 95.

[231] Renner et al. (2016), p. 95.

[232] EMA, Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products, 30 May 2008, EMEA/CHMP/GTWP/125491/2006, available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-requirements-environmental-risk-assessment-gene-therapy-medicinal-products_en.pdf (accessed 25 Feb 2021).

[233] GCP Ordinance, § 9(4); cf. Genetic Engineering Act, §§ 14(1), 31.

[234] Renner et al. (2016), p. 97.

For the ethical evaluation, there are currently 35 registered ethics committees.[235] They have all been established by the *Länder* and have been authorised by the Federal Institute for Drugs and Medical Devices together with the PEI.[236] The ethics committee must be provided with comprehensive documentation that allows for an assessment of the risk-benefit balance[237] as well as the surveillance of the procedure of obtaining informed consent and that proves the adequacy and completeness of the written information given to the patient for this purpose.[238]

The procedure is structured in a similar way to the one for scientific evaluation: The sponsor's application is examined for a period of 90 days. If the ethics committee does not have expert knowledge of its own in the field of GTMPs, it has to consult experts or request expert opinions. In this case, the maximum period is 180 days.[239] The ethics committee may request additional information. Until the sponsor complies with the request, the evaluation period is suspended.[240]

In the case of multi-centre trials, the ethical evaluation is directed by the ethics committee responsible for the principal centre, i.e. the centre of the chief investigator. The ethics committee in charge reaches its decision in consultation with the ethics committees responsible for the other centres.[241] This procedure ensures the participation of all competent ethics committees, while at the same time avoiding contradictory decisions.

3.3.4 Administration Without Marketing Authorisation

There are several exceptions to the general rule that a medicinal product requires a marketing authorisation in order to be used for therapeutic purposes within the EU.[242]

First, medicinal products can be made available for compassionate use before they obtain a marketing authorisation (see Sect. 3.3.4.1). Second, there are two exemptions which apply to treatments of individual patients: the 'hospital exemption' which applies to ATMPs only (see Sect. 3.3.4.2) and the 'special needs exemption' which applies to any kind of medicinal products (see Sect. 3.3.4.3). Third, the administration of medicinal products outside the scope of EU pharmaceutical legislation remains at the discretion of the Member States (see Sect. 3.3.4.4).

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[235] Cf. Bundesinstitut für Arzneimittel und Medizinprodukte (2019).

[236] Medicinal Products Act, § 41a(1), (3).

[237] Directive 2001/20/EC, Art. 3(2)(a), 6(3)(b); GCP Ordinance, § 7(3) No. 2.

[238] Directive 2001/20/EC, Art. 6(3)(g); GCP Ordinance, § 7(3) No. 9.

[239] Directive 2001/20/EC, Art. 6(7); Medicinal Products Act, § 42(1); GCP Ordinance, § 8(4).

[240] Directive 2001/20/EC, Art. 6(6); GCP Ordinance, § 8(2).

[241] Directive 2001/20/EC, Art. 7[1]; Medicinal Products Act, § 42(1); GCP Ordinance, § 8(5).

[242] Cf. Dederer and Frenken (2021), pp. 47–52.

3.3.4.1 Compassionate Use

The EMA regulation enables the Member States to allow the compassionate use of medicinal products whose marketing authorisation is granted in the centralised procedure.[243] The compassionate use programme is not designed as an alternative to the regular marketing authorisation but as a possibility to benefit from innovative medicinal products for patients who could not be included in clinical trials. Therefore, it only applies to medicinal products which are undergoing clinical trials or for which a marketing authorisation application has been submitted to the EMA. These medicinal products can be made available "for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactorily by an authorised medicinal product".[244]

Germany has incorporated the possibility of a compassionate use into the Medicinal Products Act as an exception to the general requirement of a marketing authorisation.[245] In order to prevent the misuse of the compassionate use programme for circumventing the general authorisation requirement, the medicinal products must be made available free of charge.[246]

The procedure relating to the compassionate use has been determined in the Cases of Hardship Ordinance.[247] Any compassionate use has to be notified to the PEI.[248] The notification has to be accompanied by various particulars and documents, inter alia the results of clinical trials,[249] an environmental risk assessment[250] and a justification why the patients could not be included in an ongoing clinical trial.[251] Within 2 weeks, the PEI confirms the receipt of the notification.[252] For ATMPs, this time-limit can be extended to a maximum period of 60 days. If the PEI does not object (which it can only do if the requirements for a compassionate use are not met or if there are indications that the information provided is incorrect or that the safe use of the medicinal product is not guaranteed),[253] the compassionate use may be

[243] Regulation (EC) No 726/2004, Art. 83(1).

[244] Regulation (EC) No 726/2004, Art. 83(2).

[245] Medicinal Products Act, § 21(2) No. 6.

[246] Medicinal Products Act, § 21(2) No. 6, cf. Deutscher Bundestag (2009), p. 47.

[247] Ordinance on the placement on the market of medicinal products without license or without marketing authorisation in cases of hardship *(Arzneimittel-Härtefall-Verordnung)* of 14 July 2010 (Federal Law Gazette Part I p. 935). Regrettably, there is no English translation available.

[248] Cases of Hardship Ordinance, § 3(1).

[249] Cases of Hardship Ordinance, § 3(2) No. 8.

[250] Cases of Hardship Ordinance, § 3(2) No. 11.

[251] Cases of Hardship Ordinance, § 3(2) No. 6.

[252] Cases of Hardship Ordinance, § 4(1).

[253] Cases of Hardship Ordinance, § 4(3).

commenced after the applicant has been notified the confirmation of the receipt of the notification.[254]

3.3.4.2 Hospital Exemption

The ATMP Regulation amended the Directive on the Community code relating to medicinal products for human use introducing a new exemption from the scope of the Directive and, thus, an exception to the applicability of the centralised procedure for granting a marketing authorisation: the so-called 'hospital exemption'.

> This Directive does not apply to any advanced therapy medicinal product [. . .] which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.[255]

The hospital exemption's scope can be divided into several elements which, in turn, can be grouped into two major categories: preparation and use.

To fall within the scope of the hospital exemption, the preparation of a medicinal product has to occur in an individualised manner, i.e. the product must be produced to an individual order, the medical prescription, and not be kept in stock.[256]

The decisive criterion for the scope of the hospital exemption is that the medicinal product must be prepared on a non-routine basis. Neither the EU law nor the European Court of Justice have further specified how to interpret the "non-routine basis".

Understanding the preparation on a non-routine basis as the opposite of the industrial preparation or the manufacture by a method involving an industrial process—which is required for the applicability of the EU's pharmaceutical legislation[257]—would deprive the hospital exemption of any effect. Medicinal products that are neither prepared industrially nor manufactured by a method involving an industrial process do not fall under EU law from the outset. Hence, there is no necessity to exempt them explicitly.[258] Therefore, such an interpretation should be ruled out.[259]

Consequently, there are basically two possibilities of interpreting the 'non-routine basis' requirement. On the one hand, a quantitative approach would focus on the scale of manufacture. The most rigid way would be to limit the quantity to an absolute number. In a more dynamic form, scale and frequency of manufacture would together be considered over a certain period of time. On the other hand, an

[254] Cases of Hardship Ordinance, § 4(2).

[255] Directive 2001/83/EC, Art. 3 No. 7.

[256] Bock (2012a), p. 133; cf. Medicinal Products Act, § 4b(1) No. 1.

[257] Cf. Directive 2001/83/EC, Art. 2(1); for details see Sect. 3.2.3.

[258] Cf. Bock (2012a), p. 134.

[259] Cf. Bock (2012a), p. 135.

impact-based approach would focus on the hospital exemption's assumed aim of providing the possibility of using ATMPs which are prepared on such a small scale that sufficient data for a comprehensive evaluation of the medicinal product by the EMA cannot be gained. Scale and frequency of manufacture would only be taken as an indication of the fact that the evaluation of a certain ATMP is not possible.

Germany has followed the second approach: an ATMP is considered to be prepared on a non-routine basis if it is manufactured and used on such a small scale and frequency that it is not possible, or has not yet been possible, to collect the necessary data for a comprehensive evaluation of the product in the centralised procedure.[260]

The preparation according to "specific quality standards"[261] is legally defined. ATMPs falling within the hospital exemption's scope must comply with standards "equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which [a regular marketing authorisation] is required",[262] i.e. they must adhere to the principles and guidelines of GMP.[263] Hence, the preparation according to "specific quality standards" must not be understood as a delimitation of the hospital exemption's scope but as a requirement for ATMPs falling within that scope.

To fall under the hospital exemption, the medicinal product has to be used in a hospital in the Member State in which it has been produced. EU law usually distinguishes the terms "hospital", "institution" and "private practice"[264] (sometimes denominated as "hospital", "health centre" and "clinic").[265] Assuming that these terms are used interchangeably with the same meaning within one and the same legal text, one can conclude that the use of the medicinal product in an institution or private practice is not covered by the hospital exemption. It has to take place in a hospital, i.e. a place for (stationary) treatment and care.[266]

Nevertheless, the German Medicinal Products Act requires the AMTP to be used "in a specialised facility for health care". It has been claimed that this incorporation of the hospital exemption into German law was contrary to the Directive on the Community code relating to medicinal products for human use.[267] Indeed, the "facility for health care" in the German Medicinal Products Act could be defined

[260] Medicinal Products Act, § 4b(2) No. 1, 2.

[261] Cf. Medicinal Products Act, § 4b(1) No. 2.

[262] Directive 2001/83/EC, Art. 3 No. 7.

[263] Cf. Bock (2012a), p. 181; Faltus (2016), pp. 716–717.

[264] Cf. Directive 2001/83/EC, Art. 71(3), Annex I Part I par. 5.2. c), Part IV par. 3.1.; Regulation (EC) No 1394/2007, Art. 15(1), (2), (3).

[265] Regulation (EU) No 536/2014, Art. 61(5)(a), (b), (c).

[266] Cf. Hornby (2010), entry "hospital".

[267] Cf. Bock (2012a), p. 193; Bock (2012b) p. 794.

by the Transfusion Act[268] as "hospital or other medical facility that treats persons".[269] In this case, its meaning would be broader than the one of the term "hospital" in the European directive. Such an approach must be rejected, though, as it ignores the key principle of interpreting and applying the legislation implementing a European directive "in conformity with the requirements of Community law".[270] This obligation to interpret national law in accordance with the directives, which the European Court of Justice has developed in its settled case-law, has been broadly taken up in legal literature.[271] In essence, national law must be interpreted according to the principle of *effet utile*[272] and with the aim of obtaining the result determined by the European directive wherever this is possible. In Germany, such an interpretation is possible if it is not contrary to the wording. Even an interpretation *contra legem* might be permitted as long as it does not contravene the legislature's intentions.[273] As neither the wording nor the systematic argument mentioned above (the reference to definition in the Transfusion Act) preclude such an interpretation, the meaning of the "specialised facility for health care" in German law must be equated with the one of "hospital" in European law: a place for (stationary) treatment and care.[274]

Furthermore, the administration has to take place under the "exclusive professional responsibility" of a medical practitioner,[275] which has to be distinguished from the "direct personal responsibility"[276] required under the special needs exemption.[277] Hence, as the responsibility can be indirect, the medical practitioner may be assisted and may even delegate his/her obligation to supervise the assisting staff.[278] Hence, vertical division of labour is permitted. In contrast, horizontal division of labour is explicitly ruled out. As the responsibility has to be "exclusive", it cannot be shared by various medical practitioners of equal rank.

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[268] Transfusion Act *(Transfusionsgesetz)* in the version published on 28 August 2007 (Federal Law Gazette Part I p. 2169), last amended by Article 20 of the Act of 20 November 2019 (Federal Law Gazette I p. 1626). Regrettably, there is no English translation available.

[269] Transfusion Act, § 14(2).

[270] ECJ, Judgement of 10 April 1984, *von Colson and Kamann v Land Nordrhein-Westfalen*, C-14/83, EU:C:1984:153, par. 26, par. 3 of the operative part; ECJ, Judgement of 10 April 1984, *Harz v Deutsche Tradax GmbH*, C-79/83, EU:C:1984:155, par. 26, par. 3 of the operative part.

[271] Cf. Kühling (2014), p. 482.

[272] TEU, Art. 4(3); cf. ECJ, Judgement of 4 December 1974, *van Duyn v Home Office*, C-41/74, EU:C:1974:133, par 12.

[273] Cf. Kühling (2014), p. 485.

[274] The same conclusion—but based on the opposite reasoning—is drawn by Gasser and Spranger (2020), pp. 131–132, who stick to the definition of the "facility of health care" as "hospital or other medical facility that treats persons"—which they then equate with the meaning of "hospital" in EU law, as this term is not legally defined.

[275] Cf. Medicinal Products Act, § 4b(1) No. 3.

[276] Directive 2001/83/EC, Art. 5(1).

[277] See Sect. 3.3.4.3.

[278] Cf. Bock (2012a), p. 188.

The hospital exemption constitutes an exception to the applicability of the general pharmaceutical legislation. The Directive on the Community code relating to medicinal products for human use does not apply to ATMPs falling within the hospital exemption's scope. Neither the Member State's obligation to establish a manufacture authorisation requirement nor the centralised procedure for obtaining a marketing authorisation are applicable.

Nevertheless, the regulation of ATMPs falling under the hospital exemption is not completely left to the discretion of the Member States. The latter are obliged to impose the requirement of a manufacture authorisation—which does not have to be identical to the one for ATMPs produced on a routine basis—and to ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards are equivalent to those applying to ATMPs whose marketing is authorised in the centralised procedure.[279] It is worth noting that the Member States are not compelled to impose any kind of authorisation of the medicinal product itself.

However, this is the regulatory approach Germany has chosen. In addition to the regular manufacture authorisation,[280] ATMPs falling within the hospital exemption's scope require a specific product-based licence *(Genehmigung)* granted by the PEI under § 4b of the Medicinal Products Act.[281]

The procedure for obtaining the licence is initiated by an application which must be accompanied by various particulars and documents, including a risk-benefit assessment,[282] the results of pharmaceutical (microbiological, chemical, biological or physical)[283] and pre-clinical (toxicological and pharmacological) tests[284] as well as an environmental risk assessment.[285] The most significant difference to the application for a marketing authorisation in the centralised procedure is that the results of clinical trials are not necessary for obtaining the licence.[286] The PEI takes its decision on the application within 5 months.[287] This time limit is suspended if the PEI asks the applicant to correct flaws until the applicant has complied with the request or until the deadline set for the correction has expired.[288]

The PEI's decision on the application is based on a risk-benefit evaluation which considers the preliminary data on quality, safety and efficacy of the medicinal

[279] Directive 2001/83/EC, Art. 3 No. 7[2].

[280] Cf. Medicinal Products Act, § 13(1), which does not exempt ATMPs falling under the hospital exemption from the general requirement of a manufacture authorisation—see Sect. 3.3.2.

[281] Medicinal Products Act, §§ 4b(3), 77(2).

[282] Medicinal Products Act, §§ 4b(3), 21a(2) No. 11.

[283] Medicinal Products Act, §§ 4b(3), 21a(2) No. 9.

[284] Medicinal Products Act, §§ 4b(3), 21a(2) No. 10.

[285] Medicinal Products Act, § 4b(3) No. 5.

[286] This results from an *argumentum e contrario* with §§ 4b(3), 21a(2) No. 9 and 10 of the Medicinal Products Act.

[287] Medicinal Products Act, §§ 4b(3), 21a(4).

[288] Medicinal Products Act, §§ 4b(3), 21a(4).

product.[289] As the licence comprises the deliberate release authorisation required under GMO legislation, the PEI reaches its decision in consultation with the Federal Office of Consumer Protection and Food Safety,[290] which means that the latter must be given the opportunity to submit a non-binding opinion.[291]

3.3.4.3 Special Needs Exemption

Besides the hospital exemption, another provision exists that allows the Member States to deviate from EU pharmaceutical law: the special needs exemption.

> A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.[292]

Unlike the hospital exemption, the special needs exemption is not limited to ATMPs. As its scope is much wider and exempted medicinal products are not subject to any constraints, its potential for circumventing the hospital exemption's restrictions cannot be denied. However, Germany has not made use of the special needs exemption. Therefore, in Germany, this provision is not relevant in the context of combined gene/cell therapy.

3.3.4.4 Point-of-Care Treatment

Finally, medicinal products may be administered without marketing authorisation in constellations of point-of-care treatment, i.e. in the case that the treating physician removes, manufactures and administers the cells himself/herself. If the entire process is carried out by one person—or at least under the responsibility of one and the same person—the power of disposal of the cells is not transferred at any time, the medicinal product is thus not distributed and consequently not placed on the market. Therefore, no marketing authorisation is required.[293]

As the constellations of point-of-care treatment do not fall within the scope of EU pharmaceutical law, their regulation is at the discretion of the Member States. In Germany, the administration of medicinal products entirely manufactured by the treating physician does not require an authorisation. However, in this case the

[289] Cf. Medicinal Products Act, §§ 4b(3), 21a(6).

[290] Medicinal Products Act, § 4b(4).

[291] Cf. Weber (2019), entry "Einvernehmen".

[292] Directive 2001/83/EC, Art. 5(1).

[293] See Sect. 3.2.3; cf. Faltus (2020), pp. 69–70.

physician requires a manufacture authorisation (which covers the biopsy of the cells, too).[294] In addition, if the medicinal product is, or contains or consists of, a GMO that is, or might be, deliberately released into the environment, the Federal Office of Consumer Protection and Food Safety must authorise the deliberate release.[295]

Furthermore, in 2019, the pharmacovigilance for ATMPs that do not require an authorisation have been substantially tightened. First, any therapeutic use has to be notified to the PEI.[296] However, quality, safety and efficacy of the medicinal product are not evaluated. Second, the treating physician is obliged to record all suspected adverse reactions and to report information on all serious suspected adverse reactions to the authorities established for the execution of the Medicinal Products Act by the *Länder*, which forward the notification to the PEI.[297]

3.4 Treatment of the Patient's Genetic Data

In combined gene/cell therapy as it is discussed in this chapter, human cells are reprogrammed into iPS cells which are then genome-edited via, e.g., CRISPR-Cas and finally re-differentiated into somatic cells (or progenitor cells). To assess the quality of these cells, which are regulated as GTMPs, they have to be tested for off-target effects as an unintended result of the use of genome editing techniques and for any other genetic aberrations due to the reprogramming process. To this aim, a full screening of the genome might be necessary to rule out, e.g., tumorigenicity,[298] of the administered cells. In this context, in case of an autologous cell/gene therapy, the question arises of how the patient's genetic data are treated.

3.4.1 Special Status of Genetic Data

Any considerations depart from the fact that genetic data are attributed a special status. This concept—which is denominated "genetic exceptionalism"—is frequently defended in legal literature[299] though it has also been considerably criticised.[300] It constitutes the basis of the German legislature's approach to this

[294] See Sects. 3.3.1 and 3.3.2, Faltus (2020), p. 69.

[295] Directive 2001/17/EC, Art. 6(1); Genetic Engineering Act, § 14(1) No. 1.

[296] Medicinal Products Act, § 67(9).

[297] Medicinal Products Act, § 63j(1), (3).

[298] Cf. Sato et al. (2019).

[299] Cf. Linoh and Rosenau (2020), p. 1; Vossenkuhl (2013), pp. 93–97; Heyers (2008), p. 508; Deutscher Bundestag (2008), p. 16; Damm and König (2008), p. 65; Lindner (2007), p. 287; cf. UNESCO International Declaration on Human Genetic Data of 16 October 2003, Art. 4.

[300] Cf. Eberbach (2010), p. 162; Kiehntopf and Pagel (2008).

matter.[301] European Union legislation reflects it as well when regulating genetic data under the provisions for 'special categories of personal data', a euphemism for particularly sensitive data.[302]

The special status of genetic data originates in their significantly increased predictive potential in comparison to other medical data, which allows for pre-symptomatic statements about disease dispositions.[303] The results from genetic analyses do not only affect the person whose genes have been examined but also enable conclusions to be drawn about his or her close relatives.[304] The knowledge gained from genetic examinations is, in principle, immutable and retains its validity for the entire life of the individual—and even for further generations.[305] It may lead to sweeping changes in the personal way of life and future plans and cause severe depressions.[306] Finally, certain knowledge of genetic characteristics poses a risk of social discrimination, stigmatisation and exclusion.[307] From a technical point of view, it must be added that the uniqueness of the so-called genetic fingerprint makes the anonymisation of genetic data difficult, if not impossible.[308] Due to this characteristics, the analysis of genetic data and the knowledge gained from such an examination may have a particular impact on fundamental rights.[309]

3.4.1.1 The Fundamental Right to Informational Self-Determination

Under the German Constitution, the Basic Law, genetic data are protected by the fundamental right to informational self-determination,[310] which was developed by

[301] Deutscher Bundestag (2008), p. 16.

[302] Cf. Weichert (2017), p. 538, see Sect. 3.4.1.2.

[303] Linoh and Rosenau (2020), p. 1; Vossenkuhl (2013), pp. 93–97; Heyers (2008), p. 508; Deutscher Bundestag (2002), p. 131; Damm and König (2008), p. 65; Lindner (2007), p. 287.

[304] Heyers (2008), p. 508; Deutscher Bundestag (2008), p. 16; Lindner (2007), p. 287; Deutscher Bundestag (2002), p. 131.

[305] Hübner and Pühler (2010), p. 678; Heyers (2008), p. 508; Deutscher Bundestag (2002), p. 131.

[306] Heyers (2008), p. 508; Deutscher Bundestag (2002), p. 131.

[307] Deutscher Bundestag (2008), p. 16; Lindner (2007), p. 287; Deutscher Bundestag (2002), pp. 131–132.

[308] Weichert (2017), p. 540; Vossenkuhl (2013), pp. 94, 97.—On the contrary, Marnau et al. (2018), p. 87, defend that the anonymisation of genetic data is possible because, from a legal point, it must only be effective, but not absolute.

[309] Heyers (2008), p. 508; Lindner (2007), p. 287; cf. Weichert (2017), pp. 539–540.

[310] German Federal Constitutional Court (BVerfG), Chamber Order of 14.12.2000, 2 BvR 1741/99, 276/00, 2061/00, BVerfGE 103:21–41, par. 49; Deutscher Bundestag (2008), p. 16, cf. Lindner (2007), p. 290; Kluth (2003), pp. 89–92; Deutscher Bundestag (2002), p. 137; cf. Scherrer (2012), pp. 320–344.—As genetic data are biological data, it could be assumed that they were protected by a fundamental right to '*bio*-informational self-determination' (cf. Duttge (2011), p. 2). However, the correct designation for the fundamental right as it was developed by the Federal Constitutional Court is 'informational self-determination'. Genetic data merely represent a particular form of data protected under this fundamental right.—On the contrary, the terms 'gene-informational self-

the Federal Constitutional Court in 1983. In the census judgement *(Volkszählungsurteil)*, the Court held that the general right of personality[311] encompasses the individual's protection against unlimited collection, storage, use, and sharing of personal data.[312] The fundamental right to informational self-determination guarantees the power conferred on individuals to, in principle, decide themselves whether and to what extent to disclose aspects of their personal life.[313] It is, in its dogmatic origins, a subjective right in defence against the state. The collection, storage and sharing of data by the state as well as any use, in particular any (automatic) processing,[314] without consent of the concerned individual constitute an encroachment on the right of informational self-determination.

Nevertheless, an encroachment can be justified. The right to informational self-determination may be restricted by law or pursuant to a law, which—according to the principles of rule of law (*Rechtsstaat*) and democracy—must consist in an Act of Parliament.[315] Apart from the principle of proportionality,[316] two principles are of major importance in this context. On the one hand, the principle of clarity demands that the adopted provisions are transparent and understandable. On the other hand, the principle of certainty requires the law to detail the type of data it refers to, the purposes for which the data can be processed and the allowed operations of processing.[317] The constitutionally required degree of detail depends on various factors, e.g. the extent to which data are collected, the sensitivity or relevance of the collected data for the personality, the possibility of alignment or combination with other data and the effects on uninvolved people.[318] Frequently, these requirements lead to highly complex norms, which conflicts with the principle of specificity.[319]

Apart from its function as subjective right, the fundamental right to informational self-determination is also objective law. Hence, the state is called upon to protect the individuals' right to decide themselves on the disclosure and use of their personal data vis-à-vis other individuals. This constitutes the basis for data protection law,

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determination' (Begemann (2015), pp. 103 et seq.), 'genetic self-determination' (Halàsz (2004), p. 86) or 'right to one's own genetic code' (Fisahn (2001), p. 52–53) refer to broader concepts which often encompass the relation between the individual and its own genetic data (e.g. a right to know and/or not to know).

[311] Basic Law, Art. 2(1) in conjunction with Art. 1(1).

[312] BVerfG, Judgement of 15 December 1983, 1 BvR 209, 269, 362, 420, 440, 484/83, BVerfGE 65:1–71, par. 147.

[313] BVerfG, Judgement of 15 December 1983, 1 BvR 209, 269, 362, 420, 440, 484/83, BVerfGE 65:1–71, par. 147.

[314] BVerfG, Order of 18 December 2018, 1 BvR 142/15, BVerfGE 150:244–309, par. 45.

[315] Rademacher and Perkowski (2020), p. 719.

[316] Lorenz (2008), par. 339.

[317] Kingreen and Kühling (2015), pp. 215–216.

[318] Lorenz (2008), par. 343.

[319] Kingreen and Kühling (2015), pp. 215–216.

which is aimed to protect the right to informational self-determination against the collection, storage, use, and sharing of personal data by other individuals.[320]

3.4.1.2 Genetic Data in General Data Protection Law

On EU level, the equivalent to the (German) fundamental right to informational self-determination in the Charter of Fundamental Rights of the European Union[321] is the right to the protection of personal data.[322] As regards legislative powers, the EU and the Member States share the competence for "the protection of individuals with regard to the processing of personal data by Union institutions, bodies, offices and agencies, and by the Member States when carrying out activities which fall within the scope of Union law, and [for] the free movement of such data".[323]

Based on this competence title, the EU has adopted the General Data Protection Regulation.[324] It defines genetic data as "personal data relating to the inherited or acquired genetic characteristics of a natural person which give unique information about the physiology or the health of that natural person and which result, in particular, from an analysis of a biological sample from the natural person in question".[325] They are regulated under the provisions on "special categories of personal data",[326] i.e. particularly sensitive data.[327] The lawfulness of the processing of genetic data is subject to requirements which are stricter than the general ones: if the processing is based on the person's consent, the consent has to be given explicitly.[328] If the person is incapable of giving consent, genetic data may only

[320] BVerfG, Judgement of 13 February 2007, 1 BvR 421/05, BVerfGE 117:202–244, par. 67; Lindner (2007), p. 292; cf. (restrictive) Kluth (2003), p. 92.

[321] Charter of Fundamental Rights of the European Union [2016], OJ C 202, 7.6.2016, p. 389 (CFR), available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:12016P/TXT&from=EN (accessed 25 Feb 2021).

[322] CFR, Art. 8(1); cf. TFEU, Art. 16(1).

[323] TFEU, Art. 16(2), 4(1).—It could be argued, though, that the EU has exclusive competence for, at least, the protection of individuals with regard to the processing of personal data by EU institutions, bodies, offices and agencies by virtue of the nature of this matter as only the EU itself (and not the Member States) can legislate on the action taken by its organs.

[324] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (OJ L 119, 4.5.2016, p. 1). A consolidated version of 04.05.2016 is available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02016R0679-20160504&from=EN (accessed 25 Feb 2021).

[325] Regulation (EU) 2016/679, Art. 4 No. 13.

[326] Regulation (EU) 2016/679, heading of Art. 9.

[327] Cf. Weichert (2017).

[328] Regulation (EU) 2016/679, Art. 9(2)(a) as *lex specialis* to Art. 6(1)(a), 7(1), (2); see Spranger (2017), pp. 864–865.—However, the EU and the Member States may determine circumstances

be processed in order to protect "vital interests".[329] Otherwise, the processing of genetic data is only permitted in exceptional cases, inter alia for the purposes of preventive medicine, medical diagnosis, the provision of health care or treatment,[330] for reasons of public interest in the area of public health (notably for "ensuring high standards of quality and safety of health care and of medicinal products")[331] and for achieving purposes in the public interest, scientific or historical research purposes or statistical purposes.[332]

The Member States are entitled to "maintain or introduce further conditions, including limitations, with regard to the processing of genetic data".[333] Germany has used this power by regulating data processing for purposes of scientific or historical research and for statistical purposes in the Federal Data Protection Act.[334] The processing of, inter alia, genetic data is permitted also without consent for scientific or historical research purposes or statistical purposes if it is necessary for these purposes and the interests in processing substantially outweigh those of the data subject in not processing the data.[335] In this case, the genetic data shall be rendered anonymous as soon as the research or statistical purpose allows, unless this conflicts with legitimate interests of the data subject. Until such time, the genetic data shall be pseudonymised.[336]

3.4.2 Specific Provisions for Genetic Data

In addition to the general provisions of data protection law, Germany has enacted specific legislation on genetic data.

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under which it is not possible to consent to the processing of genetic data (Regulation (EU) 2016/679, Art. 9(2)(a)).

[329] Regulation (EU) 2016/679, Art. 9(2)(c) as *lex specialis* to Art. 6(2), (3).

[330] Regulation (EU) 2016/679, Art. 9(2)(h).—In these cases, the genetic data must be processed "by or under the responsibility of a professional subject to the obligation of professional secrecy" (Regulation (EU) 2016/679, Art. 9(3)).

[331] Regulation (EU) 2016/679, Art. 9(2)(i).

[332] Regulation (EU) 2016/679, Art. 9(2)(j).—In these cases, the processing must comply with the requirements in Art. 89.—Halàsz (2004), pp. 195–196, argues that, in the light of the overall scheme and objectives of EU data protection law, the requirement of consent takes priority over the (exceptional) permission of data processing for research purposes, which therefore can only apply subsidiarily under special circumstances.

[333] Regulation (EU) 2016/679, Art. 9(4).

[334] Federal Data Protection Act *(Bundesdatenschutzgesetz)* of 30 June 2017 (Federal Law Gazette Part I p. 2097), last amended by Article 12 of the Act of 20 November 2019 (Federal Law Gazette I p. 1626). An English translation is available at https://www.gesetze-im-internet.de/englisch_bdsg/englisch_bdsg.pdf (accessed 25 Feb 2021).

[335] Federal Data Protection Act, § 27(1).

[336] Federal Data Protection Act, § 27(3).

3.4.2.1 The Genetic Diagnostic Act

In 2009, Germany adopted the Genetic Diagnostic Act *(Gendiagnostikgesetz)*.[337] It serves the purpose of fulfilling the German state's positive obligation to protect the right to informational self-determination.[338] The Genetic Diagnostic Act applies to genetic examination and genetic analysis.[339] While the term "genetic analysis" refers to the biotechnical process itself,[340] the term "genetic examination" is used to describe the genetic analysis for a certain purpose, which includes the evaluation of the result.[341] The Genetic Diagnostic Act covers genetic examinations for medical purposes (i.e. diagnostic or predictive genetic examinations)[342] as well as for any other purpose. However, genetic examinations for research purposes are explicitly excluded from the scope.[343] In the context of the fundamental freedom of science and research, research is defined as the process of gaining new knowledge in a methodical, systematic and verifiable manner.[344] This definition can also be adhered to when interpreting the Genetic Diagnostic Act.[345] It comprises basic research as well as applied (i.e. clinical) research.[346]

However, delimitation problems arise where genetic examinations are carried out with both an (individual) therapeutic aim and the aim of generating new knowledge—which is the case, e.g., in clinical trials but also in (experimental) individual medical treatment. If these cases were not covered by the Genetic Diagnostic Act, they would only be regulated under general data protection law as no specific legislation on genetic examinations for research purposes exists (except for clinical trials, which are governed by the Medicinal Products Act). The prevailing opinion in legal literature solves this question by asking for the main purpose of the genetic examination. If, on the one hand, the genetic examination is primarily aimed at gathering empirical data on medical treatments (as it is the case with clinical trials or clinical studies), it is considered to be done for research purposes and, therefore, to fall under the exception from the Genetic Diagnostic Act. If, on the other hand, the genetic examination is primarily aimed at the treatment of a patient (as it is the case with experimental individual medical treatment), it is not considered to be done for

[337] Genetic Diagnostic Act *(Gendiagnostikgesetz)* in the version published on 31 July 2009 (Federal Law Gazette Part I pp. 2529, 3672), last amended by Article 23 of the Act of 20 November 2019 (Federal Law Gazette I p. 1626). Regrettably, there is no English translation available.

[338] Genetic Diagnostic Act, § 1.

[339] Genetic Diagnostic Act, § 2(1).

[340] Genetic Diagnostic Act, § 3 No. 2.

[341] Genetic Diagnostic Act, § 3 No. 1.

[342] Genetic Diagnostic Act, § 3 No. 6, 7, 8.

[343] Genetic Diagnostic Act, § 2(2).

[344] Gärditz (2020), par. 94 referring to BVerfG, Judgement of 29 May 1973, 1 BvR 424/71, 325/72, BVerfGE 35:79, p. 113.

[345] Linoh and Rosenau (2020), pp. 2–3.

[346] Cf. Gärditz (2020), par. 106–107.

research purposes regardless of whether new knowledge is gained. Consequently, the provisions of the Genetic Diagnostic Act are applicable.[347]

Genetic examinations for medical purposes are governed by Chapter 2 of the Genetic Diagnostic Act. The genetic examination must be carried out by a medical practitioner[348] who, however, may delegate the genetic analysis itself.[349] The patients are informed about nature, significance and implications of the genetic examination.[350] This information comprises, inter alia, the purpose of the examination, possible risks and the intended use of the genetic sample and of the results of the examination or analysis.[351] After a reasonable reflection period,[352] the patients have to give their informed consent explicitly and in writing, which includes the decision on the scope of the examination, on the extent to which the patient is informed about the results and on the destruction of the latter.[353] The consent may be withdrawn at any time.[354]

The genetic sample may only be used for the purpose for which it has been collected (covered by the patient's informed consent) and must be destroyed as soon as it is not needed for this purpose any longer.[355] By default, the results are retained for a period of 10 years before being destroyed. The patient may ask for a longer retention period as well as for the immediate destruction of the results.[356] If the patient withdraws his/her consent, both the genetic sample and the results of the genetic examination or analysis are destroyed immediately.[357]

3.4.2.2 Protection of Genetic Data in Clinical Trials

As shown in the previous section, clinical trials do not fall within the scope of the Genetic Diagnostic Act. However, there are specific provisions in the Medicinal Products Act which are aimed at guaranteeing the fundamental right to informational

[347] Linoh and Rosenau (2020), p. 5; Zuck (2018), par. 96; Sosnitza and Op den Camp (2011), p. 404. — Häberle (2020), § 2 par. 4, restricts the scope of the exception of genetic examinations for research purposes to "general research which does not involve concrete measures towards specific persons" [English translation by the author], i.e. to basic research; Kern (2012a), par. 14–16, goes even further suggesting an analogous application of certain provisions of the Genetic Diagnostic Act to basic research.

[348] Genetic Diagnostic Act, § 7(1).

[349] Genetic Diagnostic Act, § 7(2).

[350] Genetic Diagnostic Act, § 9(1).

[351] Genetic Diagnostic Act, § 9(2) No. 1, 2, 3.

[352] Genetic Diagnostic Act, § 9(1).

[353] Genetic Diagnostic Act, § 8(1).

[354] Genetic Diagnostic Act, § 8(2).

[355] Genetic Diagnostic Act, § 13(1).—The patient may consent to a longer retention period (Kern (2012b), par. 8; Fenger (2018), § 13 par. 1).

[356] Genetic Diagnostic Act, § 12(1).

[357] Genetic Diagnostic Act, §§ 13(1), 12(1).

self-determination in this context. Clinical trials may only be conducted if the patient has given his/her informed consent relating to the collection and processing of "health-related data" in writing.[358] To this aim, he/she is informed about the scope and purpose of data processing with a particular focus on the disclosure of the data to the sponsor and the regulatory authorities,[359] about his/her right to withdraw the consent at any time[360] and about the fact that the withdrawal of consent does hardly affect the processing of the data already collected until the declaration of withdrawal.[361] The compliance with the provisions of informed consent is reviewed by the ethics committee.[362] In communication between sponsor and regulatory authorities, personal data are generally pseudonymised.[363]

3.5 Reform Efforts

Already a few years after the Clinical Trials Directive had become fully effective in 2004,[364] concerns were raised over its diverging application by the Member States.[365] In particular, the resulting "excessive bureaucracy" proved to be obstructive to multinational clinical trials.[366]

In response to this and on initiative of the European Commission,[367] the European Parliament and the Council adopted a new Clinical Trials Regulation on 16th April 2014, which entered into force in May 2014.[368] However, the Clinical Trials Regulation has not yet become applicable. This will occur only 6 months after the European Commission's confirmation that the new EU portal and database have achieved full functionality.[369] From this date on, the Clinical Trials Directive

[358] Medicinal Products Act, § 40(1) No. 3(c).

[359] Medicinal Products Act, § 40(2a) No. 1.

[360] Medicinal Products Act, § 40(2a) No. 2.

[361] Medicinal Products Act, § 40(2a) No. 3.

[362] GCP Ordinance, § 7(2) No. 15.

[363] GCP Ordinance, §§ 12 (4), (6), 13(1), (2), (3).

[364] Cf. Directive 2001/20/EC, Art. 22(1).

[365] European Commission (2008), p. 8.

[366] Mayor (2017).

[367] Cf. TFEU, Art. 289(1), 294(2).—For scientific advice and expertise on clinical trials, the European Commission has created the Commission Expert Group on Clinical Trials on 14th June 2006, which consists of officials of the Member States' health ministries and authorities involved in the authorisation of clinical trials; cf. European Commission (n.d.).

[368] Cf. Regulation (EU) No 536/2014, Art. 99[1].

[369] Regulation (EU) No 536/2014, Art. 99[2], 82(3), (2).

currently in force will be repealed.[370] In consequence, the provisions of the German Medicinal Products Act will become inapplicable.[371]

Whilst according to the original time frame the Clinical Trials Regulation was intended to become applicable in October 2018,[372] EMA calculated in early 2021 that the new EU portal and database would go live in December 2021.[373] According to Commission Decision (EU) 2021/1240 of 13th July 2021, the Clinical Trials Regulation will be applicable from 31st January 2022. Training sessions for the Member States' authorities began on 20th December 2020; the first training event for sponsors started on 22nd February 2021.[374]

The main objective of the Clinical Trials Regulation is further harmonisation and, thus, an enhancement of efficacy and uniformity of EU law.[375] The market availability of new medicinal products shall be guaranteed, which in turn must be seen in the broader context of improving the EU's competitiveness by fostering innovation.[376] At the same time, the protection of human subjects shall be ensured.[377]

To this aim, the scientific and ethical review of clinical trials within the EU will be fully standardised. The application dossier will be submitted through the newly developed Clinical Trial Information System (CTIS).[378] CTIS will contain the portal that will serve as single entry point for the entire communication related to clinical trials, as well as the database where this information is stored.[379] The database will be publicly accessible[380] and designed in a user-friendly manner[381] in order to meet the Clinical Trials Regulation's target of increasing transparency of clinical trial information.[382] The content of the application dossier, i.e. the required documentation and information, is listed in Annex I to the Clinical Trials Regulation.[383]

The application dossier will be scientifically reviewed by the Member States' pharmaceutical authorities and ethically reviewed by ethics committees established by the Member States.[384] It is important to emphasise that the scientific standards on which the review is based will not be altered by the new Clinical Trials Regulation.[385]

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[370] Regulation (EU) No 536/2014, Art. 96(1); cf. Regulation (EU) No 536/2014, Art. 98(1), (2) which establishes a transitional period of 3 years.

[371] Cf. ECJ, Judgement of 15 July 1964, *Costa v E.N.E.L.*, C-6/64, EU:C:1964:66.

[372] EMA (2015), p. 4.

[373] EMA (n.d.).

[374] EMA (2021a), p. 2.

[375] Flear (2016), p. 194.

[376] Flear (2016), p. 195.

[377] Cf. Regulation (EU) No 536/2014, recitals 15, 17, 27, 44, 76, 80, Art. 3, 28–35.

[378] Regulation (EU) No 536/2014, Art. 5(1)[1].

[379] Cf. Regulation (EU) No 536/2014, Art. 80, 81.

[380] Regulation (EU) No 536/2014, Art. 81(2), (4).

[381] Regulation (EU) No 536/2014, Art. 80[1].

[382] Cf. Regulation (EU) No 536/2014, recitals 25, 39, 67, 68, Art. 29(2)(b), 37(4)[2], Annex V.

[383] Regulation (EU) No 536/2014, Art. 25(1)[2].

[384] Regulation (EU) No 536/2014, Art. 4[1], [2].

[385] Gross et al. (2017), p. 826.

The assessment report itself will be divided into two parts. Part I will mainly cover scientific aspects: risks[386] and benefits[387] of the medicinal product as well as its manufacture or import[388] and labelling.[389] Hence, its assessment will not depend on local circumstances. If the clinical trial involves more than one Member State, Part I of the assessment report will be drawn up by one Member State (the so-called reporting Member State) and reviewed by the other Member States concerned. In consequence, the result will be binding for all Member States concerned,[390] which is a major improvement for the sponsor of multinational clinical trials.

Part II of the assessment report will cover aspects which are linked to ethical notions or based on local circumstances, notably informed consent,[391] recruitment and compensation of participants[392] and data protection.[393] Therefore, Part II will be carried out by each Member State concerned independently from the other Member States.[394]

It is up to the Member States to decide to what extent ethics committees shall be involved in the assessment process.[395] In Germany, the ethics committees will give their opinion on certain aspects of Part I (especially the risk-benefit-balance). This opinion will not be binding for the PEI although any deviation will have to be justified. On the contrary, the ethical evaluation, i.e. Part II of the assessment report, will remain the exclusive competence of the ethics committees without any possibility of deviating for the PEI.[396]

The assessment will be subject to strict deadlines which will be substantially tightened. Both parts of the assessment reports will be submitted to the sponsor within 45 days.[397] For Part I, there will be the possibility to extend this period by 50 days for the purpose of consulting with experts if the medicinal product is an ATMP.[398] If the sponsor is requested additional information (for which a time-limit of 12 days can be set), the assessment period will be extended by a maximum of 31 days.[399] In total, the assessment period established by the Clinical Trials

[386] Regulation (EU) No 536/2014, Art. 6(1)(b)(ii).

[387] Regulation (EU) No 536/2014, Art. 6(1)(b)(i).

[388] Regulation (EU) No 536/2014, Art. 6(1)(c).

[389] Regulation (EU) No 536/2014, Art. 6(1)(d).

[390] Regulation (EU) No 536/2014, Art. 8(2)[1].—There are only three exceptions which allow the Member States to dissent from the joint assessment, Regulation (EU) No 536/2014, Art. 8(2)[2](a)-(c).

[391] Regulation (EU) No 536/2014, Art. 7(1)(a).

[392] Regulation (EU) No 536/2014, Art. 7(1)(b), (c).

[393] Regulation (EU) No 536/2014, Art. 7(1)(d).

[394] Regulation (EU) No 536/2014, Art. 7(2)[1].

[395] Regulation (EU) No 536/2014, Art. 4[2].

[396] Nickel et al. (2017), p. 807.

[397] Regulation (EU) No 536/2014, Art. 6(4), 7(2)[1].

[398] Regulation (EU) No 536/2014, Art. 6(7).

[399] Regulation (EU) No 536/2014, Art. 6(8)[2], [3], 7(3)[1], [2].

Regulation will be a maximum of 121 days—only two thirds of the actual 180-day period.[400] Meeting the new strict deadlines is expected to be very challenging for the national authorities,[401] which might face the need to adapt their staffing.[402] The deadlines for supplementing the information and documentation submitted, on the other hand, will also result in a "mounting pressure" for the applicants, especially for smaller companies and academic researchers.[403]

3.6 Outlook: Human Germ Line Intervention through Genome Editing

EU legislation does not cover human germ line interventions through genome editing,[404] the so-called germ line editing.[405] Hence, this matter is left at the discretion of the Member States.

In Germany, the technological advances in the field of reproductive medicine and human genetics achieved in the late 1970s and 1980s led to a broad public and academic discussion.[406] In 1990, the conservative (federal) government headed by chancellor Helmut Kohl introduced a bill in order to delimit the application of the "new methods" of in vitro fertilisation and genetic engineering to human beings.[407] It was notably based on the report of the working group on in vitro fertilisation, genome analysis and gene therapy[408]—a commission set up by the Federal Ministry of Research and Technology which is informally known as the "Benda Commission" (named after its chairman Ernst Benda).[409] The report of the Parliamentarian Inquiry Commission on Opportunities and Risks of Genetic Engineering[410] and the

[400] See Sect. 3.3.3.3.

[401] Mende et al. (2017), p. 803.

[402] Abou-El-Enein and Schneider (2016), p. 231.

[403] Abou-El-Enein and Schneider (2016), p. 233.

[404] Cf. Deuring (2020), p. 53.—However, it is worth noting that the provisions on clinical trials explicitly rule out any (accidental or deliberate) modifications to the human "germ line genetic identity" (Directive 2001/20/EC, Art. 9(6); Regulation (EU) No 536/2014, Art. 90[2]); cf. Schleidgen et al. (2019), p. 10.

[405] For the terminology see National Academy of Medicine, National Academy of Sciences, Royal Society (2020), p. 18: The term "germ line (genome) editing" refers to heritable human genome editing (HHGE), i.e. "any editing in germline cells that is done in a clinical context, with the intent of transferring any resultant embryos to a woman's uterus for gestation", as well as any editing in germline cells for other, especially research purposes.

[406] Cf. Taupitz (2014) pp. 98–99.

[407] Deutscher Bundestag (1989), p. 1.

[408] Bundesminister für Forschung und Technologie (ed) (1985).

[409] Cf. Taupitz (2014), pp. 98–99.

[410] Deutscher Bundestag (1987).

report of the working group of the Federation and the *Länder* on reproductive medicine[411] also had a major influence.

The governmental bill was passed on 13th December 1990 with only minor modifications—none of them concerning the provisions for germ line editing.[412] On 1st January 1991, the Embryo Protection Act[413] entered into force. Its § 5, which regulates human germ line editing, states:

§ 5 Embryo Protection Act

(1) Anyone who artificially alters the genetic information of a human germ line cell will be punished with imprisonment up to five years or a fine.
(2) Likewise, anyone will be punished who uses a human germ cell with artificially altered genetic information for fertilisation.
(3) Any attempt is punishable.
(4) Paragraph 1 does not apply to

1. an artificial alteration of the genetic information of a germ cell situated outside the body, if any use of it for fertilisation has been ruled out,
2. an artificial alteration of the genetic information of a different body's germ line cell that has been removed from a dead embryo, from a human being or from a deceased person if it has ruled out that

   (a) they will be transferred to an embryo, foetus or human being or
   (b) a germ cell will originate from them

   and likewise
3. inoculation, radiation, chemotherapeutic or other treatment by which an alteration of the genetic information of germ line cells is not intended.

According to paragraph 1, any artificial alteration of the genetic information of a human germ line cell is forbidden. Germ line cells are defined as "all cells that lead in a cell line from the fertilised ovum to the ova and sperm cells of the resultant human being and, further, the ovum from capture or penetration of the sperm cell until the ending of fertilisation by fusion of the nuclei".[414] This definition includes the ova and sperm cells themselves.[415] Combined with paragraph 2, this results in a complete ban on heritable human genome editing.[416]

[411] Bundesminister der Justiz (ed) (1989).

[412] See also Deutscher Bundestag (1990), p. 5.

[413] Embryo Protection Act *(Embryonenschutzgesetz)* of 13 December 1990 (Federal Law Gazette Part I p. 2746), last amended by Article 1 of the Act of 21 November 2011 (Federal Law Gazette I p. 2228).

[414] Embryo Protection Act, § 8(3).

[415] Günther (2014), p. 324 par. 9; argumentum ex Embryo Protection Act, § 5(4) No. 2.

[416] Cf. Dederer and Frenken (2021), pp. 65 et seq.—The Government followed the proposition of the Benda Commission (cf. Bundesminister für Forschung und Technologie (ed) (1985), p. 47) and the parliamentarian inquiry commission (Deutscher Bundestag (1987), p. 190).

In order to guarantee the freedom of research,[417] paragraph 4 establishes an exemption: the artificial alteration of the genetic information of germ cells and germ line cells is allowed in vitro if it has been ruled out that the cells could be used for the creation of a human being. Furthermore, the alteration of human germ line cells is not punishable if it occurs as side effect of a medical treatment. Nevertheless, EU legislation on clinical trials reflects the aim of avoiding any—even unintended—alteration of germ line cells.[418]

The draft of the governmental bill for the Embryo Protection Act sets out the reasons for the actual prohibition of hereditary human genome editing.[419] The decisive argument is a pragmatic one. In 1989, genome editing techniques could not be expected to be developed without any human experiments. According to the information available at that time,[420] the risks associated with such experiments—"most severe malformations"—could not be tolerated and would infringe the fundamental right to life and physical integrity[421] as well as the guarantee of human dignity.[422] Against this background, the then government did not adopt a position towards possible categorical arguments excluding germ line editing altogether. It, nevertheless, mentioned the ("striking") dangers of misuse, in particular "for the purpose of breeding humans".[423] It should be noted that the governmental bill did not rule out the possibility that any direct intervention in the human germline could violate the human dignity which might arise from the natural origins of every human being embodied in the coincidence of their genetic information.[424] Hence, if the risks of heritable human genome editing did not exceed the risks resulting from natural mutations occurring anyway and, thus, the pragmatic arguments against germ line editing were not applicable any longer, the categorical arguments would have to be re-evaluated.[425]

Currently, the discussion has turned to human artificial gametes, i.e. gametes obtained from human iPS cells.[426] On the one hand, there seems to be general agreement about the fact that it is not possible to categorise human artificial gametes as human germ line cells.[427] Following the biological-medical meaning (which also

[417] Cf. Basic Law, Art. 5(3); see Deutscher Bundestag (1989), p. 11.

[418] Cf. Directive 2001/20/EC, Art. 9(6); Regulation (EU) No 536/2014, Art. 90(2).

[419] Deutscher Bundestag (1989), p. 11.

[420] In 1984, the success rate for hereditary genome editing in mice was still 2%, cf. Hammer et al. (1984); see Deutscher Bundestag (1987), p. 188.

[421] Cf. Basic Law, Art. 2(2).

[422] Cf. Basic Law, Art. 1(1); see Bundesminister für Forschung und Technologie (ed) (1985), p. 46.

[423] Deutscher Bundestag (1989), p. 11; see Bundesminister für Forschung und Technologie (ed) (1985), p. 46.

[424] See Deutscher Bundestag (1987), pp. 187–188.

[425] Cf. Deuring and Taupitz (2020), p. 102; Deutsch and Spickhoff (2014), p. 956.—For a multidisciplinary contribution to the discussion, see Schleidgen et al. (2019).

[426] Cf. Dederer and Frenken (2021), pp. 66 et seq.

[427] Deuring (2020), p. 105; Deuring and Taupitz (2020), p. 103; Enghofer (2018), p. 292; Müller-Terpitz (2018), § 5 par. 5; Faltus (2016), p. 462.

underlies the Embryo Protection Act[428]), artificial gametes cannot be assumed to form part of the germ line because they are derived from somatic cells. Therefore, since the Embryo Protection Act forms part of German criminal law, the prohibition of analogy in criminal law[429] does not allow to categorise human artificial gametes as human germ cells. On the other hand, until now no consensus has been reached on whether human artificial gametes can be regarded as human germ cells. The wording does not preclude such an interpretation[430]—unless germ cells are required to originate from germ line cells.[431]

3.7 Conclusion

In a globalised world, in which regulatory systems are increasingly valued as locational factors, the EU's regulatory framework for combined gene/cell therapy strikes a balance between harmonisation throughout the common market and observance of the principle of subsidiarity and between protecting patients and fostering research and innovation. In the multi-level system, the EU's legislation sets the scene, leaving various exemptions at the Member States' discretion. The EMA and national authorities interact. In Germany, the enforcement of pharmaceutical legislation is divided between the Federation, i.e. the PEI, and the authorities established by the *Länder*.

The EU in general and its Member State Germany in particular strive for maintaining high scientific and ethical standards in the field of medicinal products. Any medicinal product that is administered to a patient in Germany must comply with the principles and guidelines of GMP, regardless of whether it is placed on the market with a marketing authorisation or it is administered to the patient under any other legal regime. The same applies to medicinal products for clinical trials of all phases. In addition, clinical trials are subject to the principles of GCP. These high standards are not only in the interest of patients but ensure the scientific reliability of the results of clinical trials.

The scientific and ethical standards are enforced through a system of authorisation requirements, which covers the entire process of combined gene/cell therapy. Cell procurement for combined gene/cell therapy and manufacture of ATMPs are authorised on the national level and, within the Federal Republic of Germany, by the authorities established by the *Länder*. The marketing authorisation is granted in the centralised procedure by the European Commission on the advice of the EMA. Clinical trials—whether or not they are carried out in more than one Member State—are authorised in a decentralised way by the Member States concerned after a

[428] Embryo Protection Act, § 8(3).

[429] See Basic Law, Art. 103(2).

[430] Deuring (2020), p. 106; Deuring and Taupitz (2020), p. 106; Enghofer (2018), p. 299.

[431] Müller-Terpitz (2018), § 5 par. 5; Faltus (2016), pp. 461–462.

scientific assessment (for which the PEI is competent in Germany) and an ethical evaluation has been carried out by an ethics committee. However, the new Clinical Trials Regulation will prevent inconsistent decisions of the Member States by establishing a procedure for the joint authorisation of multi-national trials and will substantially tighten the deadlines for the assessment in order to increase competitiveness and to diminish obstacles to clinical research.

The EU's regulatory framework for ATMPs shows that setting high standards does not conflict with the goal of fostering research and innovation. To this aim, the EMA provides early and comprehensive scientific advice, notably in the PRIME scheme, and grants an accelerated assessment for innovative medicinal products. In emergency situations, it allows for a rolling review. Moreover, a conditional marketing authorisation can be granted based on preliminary evidence. The current COVID-19 pandemic has proven that this framework ensures safety, quality and efficacy of medicinal products whilst at the same time enabling a rapid reaction to public health emergencies.

With regard to the individual patient, the EU also strives for guaranteeing the availability of the best and most promising treatment. For patients who cannot be included in clinical trials, the compassionate use scheme may be available. The hospital exemption gives the Member States leeway to authorise the use of ATMPs prepared on a non-routine basis. The special needs exemption fulfils a similar function but applies to any kind of medicinal product. In Germany, the PEI is competent for granting authorisations under the hospital exemption. The special needs exemption, however, has not been incorporated into domestic law.

Finally, the regulation of point-of-care treatments is at the discretion of the Member States. Germany—considering such therapies as the exercise of the freedom of medical practice—has not imposed any authorisation requirement on such treatments. Nevertheless, the therapeutic use of ATMPs that do not require an authorisation has to be notified to the PEI.

Ultimately, the regulatory framework for combined gene/cell therapy can serve as a model that demonstrates the EU's ability to protect individuals while, at the same time, supporting economic and scientific development.

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Chapter 4
Regulation of Genome Editing in Human iPS Cells: France

Aurélie Mahalatchimy

Abstract The French legal framework on genome editing of human iPS cells is complicated as it relies on multiple applicable laws (European Union law, Council of Europe treaties, and French laws) which are under continual development. Several relevant rules can be identified regarding the access to human biological material (cells, tissues and genes and more specifically somatic cells, germ cells, embryonic cells and embryos) as well as the modalities of their use (prohibition, authorisation under specific conditions, legal gap) for specific purposes (e.g., therapy or research). These regulatory aspects are laid down primarily in EU legislation on tissues and cells and on advanced therapy medicinal products (ATMPs), as well as in French legislation implementing EU law and in the French law on bioethics. Combined gene/cell therapy using genome edited human iPS cells to be differentiated into somatic cells for autologous retransplantation is likely to be considered an application of gene therapy medicinal products either regulated at the EU level as ATMPs in case of manufacturing at an industrial scale or at the French national level under national schemes if not manufactured at an industrial scale. On the French national level, the recent revision of the French law on bioethics of 2 August 2021 provides new legal rules both for iPS cells and human genome editing.

4.1 Introduction

The French legal framework on genome editing of human iPS cells is complicated. It relies on multiple applicable laws. France is a member of the European Union and, therefore, European Union law (EU law), which is highly relevant in the field, applies.[1] EU law covers mainly the procurement and use of tissues and cells for

[1] Mahalatchimy and Rial-Sebbag (2020).

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H.-G. Dederer, G. Frenken (eds.), *Regulation of Genome Editing in Human iPS Cells*, https://doi.org/10.1007/978-3-030-93023-3_4

therapeutic applications,[2] and the entire development chain of advanced therapy medicinal products (ATMPs),[3] which is a specific legal category that includes, inter alia, medicines based on genome editing of iPS cells. EU law relating to genetically modified organisms[4] and the patentability of biotechnological inventions[5] (this last topic is beyond the scope of this report, and consequently the rules laid down in the European Patent Convention and adopted by the European Patent Office as well) is relevant as well. It also protects fundamental rights notably through the Charter of Fundamental Rights which is of a "constitutional" nature since its integration into the Lisbon Treaty.[6] In addition, France is a member of the Council of Europe and has ratified both the European Convention on Human Rights and the European Convention on Human Rights and Biomedicine (the so-called Oviedo Convention) which includes provisions that are relevant regarding the genome editing of human iPS cells such as the prohibition of genome interventions altering the descent of the person, or the right to respect for private life. Finally, France is also a sovereign state that has its own legislation on genome editing of human iPS cells, which implements EU law according to its national specificities, but also complements, and sometimes overlaps with, EU law. In this report, we will mainly focus on French law, although EU law and the treaties of the Council of Europe may also be taken into account, where relevant, as being part of the French legal order.

In addition, we have to take into account that the regulation of genome editing of human iPS cells relates to several "objects" that are regulated by different laws: the techniques of genome editing, the iPS cells, and the resultant use of the genome-edited human iPS cells, e.g. in the course of a gene or cell therapy. As a result, the French legal framework applicable to the genome editing of iPS cells is fragmented. While both genome editing and iPS cells have recently been regulated as such in French law, several relevant rules also exist regarding the access to human biological material (cells, tissues and genes and more specifically somatic cells, germ cells, embryonic cells and embryos) as well as the modalities of their uses (prohibition, authorisation under specific conditions, legal gap) for specific purposes (therapy,

[2] Mainly Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, pp. 48–58.

[3] Mainly Regulation (EC) 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) 726/2004, OJ L 324, 10.12.2007, pp. 121–137.

[4] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, OJ L 106, 17.4.2001, pp. 1–39; Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms, OJ L 125, 21.5.2009, pp. 75–97.

[5] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, OJ L 213, 30.7.1998, pp. 13–21.

[6] See notably Rosas (2012).

research).[7] These aspects are governed mainly by EU legislation on tissues and cells and on advanced therapy medicinal products (ATMPs), as well as by French legislation implementing EU law and by the French law on bioethics.[8]

Furthermore, this legal framework is always in flux. For instance, the revision of the European directive on tissues and cells is under discussion at European Union level. Moreover, the French bioethics law, which is to be revised every 7 years, has just been revised. The revision was adopted on 2 August 2021.

Apart from this regulatory landscape, it can be highlighted that France is generally known to have excellent academic research in the field of gene and cell therapy, but also to have weaknesses in translational research, notably in the transformation of research results into marketable products, due to several specific challenges for the development of regenerative medicinal products.[9] There is a similar problem at the European Union level despite a supportive regulation for the commercialization of ATMPs dating back to 2007.[10] Indeed, among the 19 ATMPs that have been authorized in the European Union (see Table 4.1 on the next page), the marketing authorisation holders of five of them decided to withdraw their marketing authorisation for commercial or business reasons (see grey coloured lines in Table 4.1).

Moreover, 17 ATMPs under the hospital exemption (MTI-PP) have been authorised in France. According to the annual reports of ANSM, five clinical trials were authorised in the field of cell therapy and 24 in the field of gene therapy in 2017,[11] and 14 in the field of gene and cell therapy in 2018.[12] Regarding national scientific advice provided in 2018, three expert opinions were on ATMPs: two on gene therapy, one on cell therapy.[13] Three research protocols on genome editing of human embryonic stem cells, using CRSIPR-Cas9 to modify the genome of human embryonic stem cells, were authorised by the Biomedicine Agency in 2016. So far, the Biomedicine Agency has not received applications for the authorisation of research protocols on genome editing of human embryos which was forbidden until 2021.

Finally, it ought to be underlined that, given the definition of iPS cells, the cells to be transformed into iPS cells are adult somatic cells. Thus, gametes and embryonic cells are not considered to be sources of iPS cells. Besides, the reprogramming of somatic cells into iPS cells that are to be differentiated into gametes or aggregated to extra-embryonic tissue in order to create embryonic entities was not comprehensively regulated by French law for research purposes (see Sect. 4.5 on Reform Efforts) and was forbidden as far as the modification of the germline was concerned

[7] The issue of intellectual property is left out as being beyond the scope of this report.

[8] Loi n° 2011-814 du 7 juillet 2011 relative à la bioéthique, JORF n°0157 du 8 juillet 2011 page 11826 texte n° 1.

[9] Gardner et al. (2015).

[10] Mahalatchimy (2011).

[11] Agence nationale de sécurité du médicament et des produits de santé (2017), p. 98.

[12] Agence nationale de sécurité du médicament et des produits de santé (2018), p. 92.

[13] Agence nationale de sécurité du médicament et des produits de santé (2018), p. 90.

Table 4.1 Advanced therapy medicinal products that have obtained a marketing authorisation in the European Union

19 AUTHORISED ATMPs IN THE EUROPEAN UNION

Name	Type	Domain	MA Year	MA Type	Orphan Status	MA Holder
Chondrocelect	TEP	Orthopaedic	2009	Normal	-	Tigenix (BE)
Glybera	GTMP	Gastrology	2012	Normal	Yes	UniQure (NL)
MACI	Comb. TEP	Orthopaedic	2013	Exceptional	-	Vericel (USA)
Provenge	CTMP	Oncology	2013	Normal	-	Dendreon/ Valeant (USA)
Holoclar	TEP	Ophthalmology	2015	Conditional	Yes	Chiesi (IT)
Imlygic	GTMP	Oncology	2015	Normal	-	Amgen Europe (NL)
Strimvelis	GTMP	Immunology	2016	Normal	Yes	GSK (UK)
Zalmoxis	CTMP	Graft vs. host	2016	Conditional	Yes	MolMed (IT)
Spherox	TEP	Orthopaedic	2017	Normal	-	CO.DON (DE)
Alofisel	TEP	Gastrology	2018	Normal	Yes	Takeda Pharma (DK)
Yescarta	GTMP	Immunocellular cancer	2018	Normal (PRIME)	Yes	Kite Pharma EU (NL)
Kymriah	GTMP	Immunocellular cancer	2018	Normal (PRIME)	Yes	Novartis Europharm (UK)
Luxturna	GTMP	Ophthalmology	2018	Normal	Yes	Spark Therapeutics (IE)
Zynteglo	GTMP	Beta-Thalassemia	2019	Conditional/Accelerated (PRIME)	Yes	Bluebird bio (NL)
Zolgensma	GTMP	Muscular Atrophy	2020	Conditional/Accelerated (PRIME)	Yes	Novartis Gene Therapies (IE)
Libmeldy	GTMP	Leukodystrophy, Metachromatic	2020	Accelerated	Yes	Orchard Therapeutics (NL)
Tecartus	GTMP	Lymphoma, Mantle-Cell	2020	Conditional/Accelerated (PRIME)	Yes	Kite Pharma EU (NL)
Skysona	GTMP	Cerebral adreno leuko-dystrophy	2021	Accelerated (PRIME)	Yes	Bluebird bio (NL)
Abecma	GTMP	Cancer of plasma cells	2021	Conditional/Accelerated (PRIME)	Yes	Celgene Europe BV (NL)

TEP: Tissue Engineered Product; GTMP: Gene Therapy Medicinal Product; CTMP: Cell Therapy Medicinal Product; MA: Marketing Authorisation, Grey: withdrawn MA

(see Sect. 4.6). In this regard, the French law on bioethics of 2 August 2021 provides new legal frameworks which open new possibilities while maintaining safeguards.

4.2 Genome Editing of Human iPS Cells: An Overview of the Regulatory Framework

The French regulatory framework relies on several legal texts and institutions both at the French and European Union level.

4.2.1 Main Applicable Legal Texts

The main applicable legal texts, which are mainly codified within the French Public Health Code, the Civil Code and the Penal Code, are the following:

- Law n° 78-17 on information technology, files and freedoms[14]
- Law n° 2011-814 on Bioethics[15], recently revised on 2 August 2021 by Law n°2021-1017 on Bioethics[16] (see Sect. 4.5 on Reform Efforts)
- Law n° 2011-2012 strengthening health safety of medicines and health products[17]
- Law n°2011-302 on several adaptations to European Union law regarding health, work and electronic communications[18]
- Law n° 2012-300 on research involving the human person[19]
- Law n°2014-201 on several adaptations to European Union law regarding health[20] (Article 6)

[14]Loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés, JORF du 7 janvier 1978, p. 227.

[15]Loi n° 2011-814 du 7 juillet 2011 relative à la bioéthique, JORF n°0157 du 8 juillet 2011 page 11826 texte n° 1.

[16]Loi n° 2021-1017 du 2 août 2021 relative à la bioéthique, JORF n°0178 du 3 août 2021 texte n° 1.

[17]Loi n° 2011-2012 du 29 décembre 2011 relative au renforcement de la sécurité sanitaire du médicament et des produits de santé, JORF n°0302 du 30 décembre 2011 page 22667 texte n° 1.

[18]Loi n° 2011-302 du 22 mars 2011 portant diverses dispositions d'adaptation de la législation au droit de l'Union européenne en matière de santé, de travail et de communications électroniques, JORF n°0069 du 23 mars 2011 page 5186 texte n° 6.

[19]Loi n° 2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine, JORF n°0056 du 6 mars 2012 page 4138 texte n° 1.

[20]Loi n° 2014-201 du 24 février 2014 portant diverses dispositions d'adaptation au droit de l'Union européenne dans le domaine de la santé, JORF n°0047 du 25 février 2014 page 3250 texte n° 4.

- Law n° 2016-41 for the modernisation of our health system[21] (Articles 149 and 155 on ATMPs)
- Law n°2017-220 simplifying the procedures of ANSM[22]
- Law n° 2018-493 on the protection of personal data[23]
- Decree n° 2016-1537 on research involving the human person[24]
- Decrees n° 2012-1236 and n° 2016-1536 on advanced therapy medicinal products[25]
- Decree n°2014-2042 on human blood[26] (Article 10)
- Decree n°2014-1066 on the conditions of procurement of organs, tissues and human cells and related activities[27]
- Decree n°2015-692 modifying several regulatory provisions on biomedical researches[28]
- Decree n°2017-389 on the conditions of cross-border exchanges of human tissues (and their derivatives) and cells and cell therapy preparations[29]
- Decree n° 2018-687 to implement the law n° 78-17 on information technology, files and freedoms as modified by Law n° 2018-493 on the protection of personal data[30]

[21] Loi n° 2016-41 du 26 janvier 2016 de modernisation de notre système de santé, JORF n°0022 du 27 janvier 2016 texte n° 1.

[22] Loi n° 2017-220 du 23 février 2017 ratifiant l'ordonnance n° 2016-966 du 15 juillet 2016 portant simplification de procédures mises en œuvre par l'Agence nationale de sécurité du médicament et des produits de santé et comportant diverses dispositions relatives aux produits de santé, JORF n°0047 du 24 février 2017 texte n° 1.

[23] Loi n° 2018-493 du 20 juin 2018 relative à la protection des données personnelles, JORF n°0141 du 21 juin 2018 texte n° 1.

[24] Décret n° 2016-1537 du 16 novembre 2016 relatif aux recherches impliquant la personne humaine, JORF n°0267 du 17 novembre 2016 texte n° 27.

[25] Décret n° 2012-1236 du 6 novembre 2012 relatif aux médicaments de thérapie innovante, JORF n°0260 du 8 novembre 2012 page 17479 texte n° 7 ; Décret n° 2016-1536 du 15 novembre 2016 relatif aux médicaments de thérapie innovante, JORF n°0267 du 17 novembre 2016 texte n° 26.

[26] Décret n° 2014-1042 du 12 septembre 2014 relatif au sang humain, JORF n°0213 du 14 septembre 2014 page 15115 texte n° 6.

[27] Décret n° 2014-1066 du 19 septembre 2014 relatif aux conditions de prélèvements d'organes, de tissus et de cellules humaines et aux activités liées à ces prélèvements, JORF n°0219 du 21 septembre 2014 page 15461 texte n° 8.

[28] Décret n° 2015-692 du 18 juin 2015 modifiant certaines dispositions réglementaires relatives aux recherches biomédicales mentionnées aux articles L. 1125-1, L. 1125-2 et L. 1125-3 du code de la santé publique, JORF n°0141 du 20 juin 2015 page 10149 texte n° 10.

[29] Décret n° 2017-389 du 23 mars 2017 relatif aux conditions d'entrée et de sortie du territoire national des tissus, leurs dérivés, des cellules issus du corps humain et des préparations de thérapie cellulaire, JORF n°0072 du 25 mars 2017 texte n° 18.

[30] Décret n° 2018-687 du 1er août 2018 pris pour l'application de la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés, modifiée par la loi n° 2018-493 du 20 juin 2018 relative à la protection des données personnelles, JORF n°0177 du 3 août 2018 texte n° 12.

- Decree n°2019-489 on hospital pharmacies[31]
- Order of 4 February 2013 on the content of applications for authorisation, renewal of authorisation, modification of authorisation of MTI-PP (exempted ATMPs) and of establishments preparing them[32]
- Orders of 28 March 2019 and 8 August 2019 limiting the use of genetically modified autologous lymphocytes T based ATMPs (CAR-T cells) treating B-cell acute lymphoblastic leukaemia or large B-cell lymphoma, to specific health establishments[33]
- Decision of 20 May 2015 on good practices of preparation, storage, distribution and transfer of MTI-PP (exempted ATMPs)[34]

The main EU legal texts applicable in France are the following:

- Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use[35]
- Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC[36]
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use[37]

[31] Décret n° 2019-489 du 21 mai 2019 relatif aux pharmacies à usage intérieur, JORF n°0119 du 23 mai 2019 texte n° 13.

[32] Arrêté du 4 février 2013 fixant le contenu des demandes d'autorisation initiale, de renouvellement d'autorisation ou de modification d'autorisation des médicaments de thérapie innovante préparés ponctuellement et des établissements ou organismes qui préparent ces produits, JORF n°0037 du 13 février 2013 page 2481 texte n° 6.

[33] Arrêté du 28 mars 2019 limitant l'utilisation de médicament de thérapie innovante à base de lymphocytes T génétiquement modifiés dits CAR-T Cells autologues indiqués dans le traitement de la leucémie aiguë lymphoblastique à cellules B et/ou du lymphome à grande cellule B, à certains établissements de santé en application des dispositions de l'article L. 1151-1 du code de la santé publique, JORF n°0085 du 10 avril 2019 texte n° 21; Arrêté du 8 août 2019 modifiant l'arrêté du 28 mars 2019 limitant l'utilisation de médicament de thérapie innovante à base de lymphocytes T génétiquement modifiés dits CAR-T Cells autologues indiqués dans le traitement de la leucémie aiguë lymphoblastique à cellules B et/ou du lymphome à grande cellule B, à certains établissements de santé en application des dispositions de l'article L. 1151-1 du code de la santé publique, JORF n°0192 du 20 août 2019 texte n° 6.

[34] Décision du 20 mai 2015 relative aux principes de bonnes pratiques de préparation, de conservation, de distribution et de cession des médicaments de thérapie innovante préparés ponctuellement définis au 17° de l'article L. 5121-1 du code de la santé publique, JORF n°0140 du 19 juin 2015 page 10100 texte n° 28.

[35] OJ L 311, 28.11.2001, p. 67.

[36] OJ L 106, 17.4.2001, pp. 1–39.

[37] OJ L 121, 1.5.2001, pp. 34–44.

- Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells[38]
- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[39]
- Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells[40]
- Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells[41]
- Regulation (EC) 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) 726/2004[42]
- Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms[43]
- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC[44]
- Regulation (EU) No 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (the so-called "GDPR").[45]

[38] OJ L 102, 7.4.2004, pp. 48–58.
[39] OJ L 136, 30.4.2004, pp. 1–33.
[40] OJ L 38, 9.2.2006, pp. 40–52.
[41] OJ L 294, 25.10.2006, pp. 32–50.
[42] OJ L 324, 10.12.2007, pp. 121–137.
[43] OJ L 125, 21.5.2009, pp. 75–97.
[44] OJ L 158, 27.5.2014, pp. 1–76.
[45] OJ L 119, 4.5.2016, pp. 1–88.

4.2.2 Competent Public Authorities

At the French national level, the main competent authorities can be distinguished according to the purposes of genome editing of human iPS cells: research purposes or therapeutic purposes.

For research purposes, the relevant provisions are scattered across various legal texts,[46] and it is necessary to distinguish between fundamental research and clinical research.

As far as fundamental research is concerned, the competent authority is the Biomedicine Agency (Agence de la Biomédecine) for embryonic stem cells as well as for certain research protocols regarding human iPS cells. The Biomedicine Agency is competent for the regulatory oversight of ethical issues considered in the bioethics law. As for embryonic stem cells, research protocols on iPS cells with the aim of differentiation of germ cells, obtaining in vitro embryonic development models, or insertion of iPS cells into an animal embryo for the purpose of its transfer to the female have to be notified to the Biomedicine Agency prior to the start of the research. For any other type of research with iPS cells that do not directly involve the human person in clinical trials, including genome editing of human iPS cells, the research protocol shall be approved by an ethics committee ('Comité de Protection des Personnes') and notified to the Ministry of Research. If the research involves the contained use (i.e., in France, the use in a research laboratory) of genetically modified micro-organisms it is required to obtain an authorisation from the Ministry of Research which will refer to the High Council of Biotechnologies (HCB) regarding the classification of the genetically modified micro-organisms. It will also contact the HCB for an opinion regarding an application for an authorisation of contained use or for information regarding a notification of contained use.[47] If the research relates to genome editing of human embryos (although it is beyond the scope of this report, it is mentioned for purposes of information), it has to be authorised under strict conditions by the Biomedicine Agency. In 2016, three research protocols on genome editing of human embryonic stem cells (using CRSIPR-Cas9 to modify the genome of human embryonic stem cells) have been authorised by the Biomedicine Agency. So far, the Biomedicine Agency has not received applications for authorisation of research protocols on genome editing of human embryos.[48]

As far as clinical research is concerned, clinical research on genome editing of human embryos and of human gametes that are to be implanted into a human person is forbidden by French law (see below Sect. 4.6). If the research concerns genome editing of human iPS cells and involves directly the human person in clinical trials, it shall be approved by an ethics committee ('Comité de Protection des Personnes') and by the French Agency for Medicines (ANSM). The same should apply to

[46] Rial-Sebbag (2019).

[47] Ministère de l'enseignement supérieur, de la recherche et de l'innovation (2013), p. 12.

[48] Le Déaut and Procaccia (2017).

genome editing of human embryonic cells although it has not been considered yet. Moreover, the HCB is involved if the investigational product contains or consists of a genetically modified organism. That applies, in particular, in the case of genome editing of iPS cells which are to be considered gene therapy products. The future clinical trial applicant shall request an opinion of HCB regarding the classification of the gene therapy product and containment measures for its handling. ANSM will also request an opinion of HCB at the time of evaluation of the respective clinical trials application.

In case of genome editing of human iPS cells for therapeutic purposes, either the European Medicines Agency and the European Commission, or the ANSM are the competent authorities depending on the classification of the product. Two main cases can be highlighted here. First, if a product based on genome editing of human iPS cells for therapeutic purposes is an advanced therapy medicinal product (ATMP) manufactured at an industrial scale to be marketed in the EU Member States, i.e. throughout the Union, it has to obtain a marketing authorisation under the European centralised procedure under EU Law (implementation of Regulation n°1394/2007 and Regulation n°726/2004). The marketing authorisation is delivered by the European Commission following an opinion by the European Medicines Agency, involving, at least, both the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Advanced Therapies (CAT). CAT has been established in 2009 following the adoption of the EU regulation n⁻1394/2007 on ATMPs. The CAT notably gives non-binding scientific opinions on the granting of marketing authorisations for products based on genome editing of human iPS cells for therapeutic purposes if they are ATMPs manufactured at an industrial scale to be marketed in the EU Member States. It also provides scientific recommendations on the classification of ATMPs. The Pharmacovigilance Risk Assessment Committee is also involved and other EMA Committees or groups may be involved in order to assist the CHMP in giving its final scientific opinion within the EMA, on the basis of which the European Commission will decide on granting marketing authorisation. Second, if a product based on genome editing of human iPS cells for therapeutic purposes is an ATMP prepared on a non-routine basis in one Member State, it is a MTI-PP that has to obtain an authorisation from the French ANSM to be applied to individual patients ('hospital exemption' or product exempted from the application of Regulation n°1394/2007).

Finally, the National Commission on information technology and freedoms (Commission nationale de l'informatique et des libertés (CNIL)) shall be consulted for the processing of health data as defined by the Regulation (EU) n°2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (the so-called "GDPR"),[49] either for authorisation or notification regarding the processing of health data for research, or if

[49] OJ L 119, 4.5.2016, pp. 188.

the processing has a public interest aim such as ensuring high quality and safety standards for medicines. (See below Sect. 4.4).

4.3 Regulatory Prerequisites for Combined Gene/Cell Therapy Using Genome Edited Human iPS Cells to Be Differentiated into Somatic Cells for Autologous Retransplantation

In France, as in the entire European Union, a combined gene/cell therapy using genome edited human iPS cells to be differentiated into somatic cells for autologous retransplantation is subject to the regulatory framework applicable to ATMPs. It includes four categories of products: gene therapy medicinal products, cell therapy medicinal products, tissue engineered products, and the combination of any of these with medical devices forming combined advanced therapy medicinal products. The genome editing of human iPS cells could be considered a substantial manipulation of the cells and, as such, the final product could be considered a somatic cell therapy medicinal product if the effect of the medicine is linked to the cell therapy and not to the genome editing. Or, more likely, the product based on the genome editing of human iPS cells could be considered a gene therapy medicinal product. In any case, only a scientific recommendation by the CAT will clarify whether a given product based on genome editing of human iPS cells is to be considered either a gene therapy medicinal product or a somatic cell therapy medicinal product, and, more generally, an ATMP or not.[50] Nevertheless, it is likely that it will be classified as an ATMP, and very probably as a gene therapy medicinal product.

Once it has been classified as an ATMP, several regulatory pathways may apply.[51]

4.3.1 The ATMP Is Manufactured at an Industrial Scale to Be Marketed in the European Union

If the ATMP is "intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process",[52] Regulation (EC) n°1394/2007 on ATMPs will apply. ATMPs must be

[50] Mourby and Morrison (2020).

[51] Mahalatchimy et al. (2012).

[52] Directive 2001/83/EC, Art. 2(1). According to the European Commission: "This should cover, inter alia: Any 'mass production' of advanced therapy products for allogeneic use (batch production, 'off the shelf' products etc.); any advanced therapy product for autologous use (i.e. using cells/tissues from a single patient and re-implanting after manipulation into same patient) which,

authorised under the centralised procedure governed by Regulation n°726/2004. Under this procedure, a company submits a single market authorization application to the EMA. The application is reviewed by the relevant scientific committee within the EMA, typically by the Committee for Medicinal Products for Human Use (CHMP), but also by the Committee for Advanced Therapies (CAT). The EMA's evaluation usually takes 210 days, following which it provides a non-binding opinion on the approval decision. The European Commission takes the final decision, which is binding throughout Europe. Until now, 19 ATMPs have been authorised in the European Union (see above Table 4.1).

In France, for ATMPs as for other medicines, the manufacturing, importation, exportation, distribution, utilisation of ATMPs have to be conducted in pharmaceutical establishments only,[53] or in public health establishments that had industrially manufactured medicines before 31 December 1991.[54] They have to obtain an authorisation from ANSM.[55]

4.3.2 The ATMP Is Not Manufactured at an Industrial Scale

If the ATMP is not manufactured at an industrial scale two different national legal schemes may apply.

4.3.2.1 The ATMP Is Covered by the So-Called 'Hospital Exemption'

ATMPs that are "prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient"[56] are not covered by the Regulation (EC) n°1394/2007 on ATMPs. Instead, they are regulated at the national level. In France, the exempted ATMPs are regulated as "Médicaments de thérapie innovante – preparés ponctuellement" (MTI-PP).

This so-called 'hospital exemption' has been implemented by all Member States. However, the individual Member States interpret and apply the hospital exemption differently, especially with regard to the notion that the exemption applies to ATMPs

although being patient-specific by definition, is manufactured in accordance with a standardised and industrial process." Commission staff working document—Annex to the proposal for a regulation on advanced therapy medicinal products impact assessment—COM (2005) 567 final/SEC/2005/1444/.

[53] Article L5124-1 of the French Public Health Code.

[54] Article L5124-9 of the French Public Health Code.

[55] Article L5124-3 of the French Public Health Code.

[56] Regulation (EC) No 1394/2007, Art. 28(2).

prepared on a "non-routine basis". In France, under the hospital exemption, an ATMP is authorised only if it is provided to a single patient at a time.

Moreover, the development of MTI-PP requires both an authorisation of the establishment and an authorisation of the product. The manufacturing, importation, exportation, distribution, utilisation of MTI-PP can be conducted in establishments, including health establishments, authorised by ANSM on the basis of an opinion by the Biomedicine Agency (the opinion is deemed affirmative if the Biomedicine Agency does not reply to ANSM within 2 months).[57] This authorisation of the establishment is issued for 5 years and can be renewed. More specifically, the authorization of the manufacturing, importation, exportation, distribution, utilisation of MTI-PP, including investigational MTI-PP, can relate to pharmaceutical establishments, health establishments, the French Establishment for Blood, or the Army Centre for Blood Transfusion. The authorization can also relate to scientific and technological public establishments, scientific cooperation foundations, foundations of public utility and associations if their object is health or biomedical research.[58] Furthermore, MTI-PP must obtain an authorisation from ANSM after assessment of their quality, safety and efficacy.[59] ANSM shall take a decision within 120 days after receiving a valid application. If ANSM does not decide within this time limit, the application is deemed to have been rejected.[60] Furthermore, if the MTI-PP includes genetically modified organisms, which is likely in the case of genome editing of iPS cells, the agreement of the Ministry of Environment and the opinion of the High Council of Biotechnologies is required.[61]

Moreover, the new French law on Bioethics eliminates certain requirements unnecessary under European Union law (need of establishment authorization to manufacture exempted ATMPs) and French Law (need of an authorization for MTI-PP). Henceforth, the preparation, distribution and administration of MTI-PP, in a health establishment or in an army hospital, as part of the same medical intervention as that of the removal of autologous tissues or cells can only be carried out under the responsibility of an establishment or organization authorized for the preparation of MTI-PP on the basis of a written agreement and with respect of good practices. A forthcoming Decree will clarify the conditions applicable to the preparation as well as the types of MTI-PP concerned.[62] In addition to ensuring compliance with other rules, be they European or French, this new provision avoids two distinct anesthesia to occur during two different medical interventions.[63]

[57] Article L4211-9-1 of the French Public Health Code.

[58] Article R4211-32 of the French Public Health Code.

[59] Article L5121-1 17° of the French Public Health Code.

[60] Article R5121-212 of the French Public Health Code.

[61] Article R5121-212 of the French Public Health Code.

[62] Article L. 4211-9-1 of the French Public Health Code.

[63] Article L. 4211-9-1 of the French Public Health Code.

4.3.2.2 The ATMP Is Covered by the Compassionate Use Schemes

In accordance with EU law, France has two particular compassionate use schemes.

First, the 'named patient' exception to the marketing authorization requirement which can be obtained from ANSM to fulfil special needs and independently from any clinical trial. This 'named provisional authorization' (*autorisation temporaire d'utilisation nominative*) is granted for medicines supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional, and intended for use by an individual patient under the direct personal responsibility of the prescribing physician.[64]

Second, the 'group' exception to the marketing authorization requirement which can be obtained from ANSM for medicines that are the subject of a pending marketing authorization application or ongoing clinical trials. This 'group provisional authorization' (*autorisation temporaire d'utilisation de cohorte*) is provided for patients with a life-threatening, or chronically or seriously debilitating disease, who cannot be treated satisfactorily by an authorised medicinal product.[65] For instance, this group provisional authorisation was granted to CAR-T cells medicines (Yescarta and Kymriah) as well as for Luxturna in France before they obtained their marketing authorisation from the European Commission.[66]

4.3.3 The ATMP Is Investigational

As for any other EU member state, clinical trials of ATMPs are currently governed by Directive 2001/20/EC,[67] which requires to conduct clinical trials in accordance with the standards of good clinical practice laid down by Directive 2005/28/EC.[68] Given the particularities of ATMPs, the European Commission also adapted guidelines on good clinical practice specific to ATMPs.[69]

By way of derogation from the regime applicable to conventional medicines, the manufacturing, importation, exportation, distribution, utilisation of investigational ATMPs can be conducted in establishments authorised by ANSM that do not have to be pharmaceutical establishments necessarily. Indeed, these activities can be conducted in any health establishment authorised for preparation, conservation,

[64] Article L5121-12 2° of the French Public Health Code.

[65] Article L5121-12 1° of the French Public Health Code.

[66] Agence nationale de sécurité du médicament et des produits de santé (2018), p. 90.

[67] Directive 2001/20/EC on good clinical practice in the conduct of clinical trials, OJ L 121/34-44.

[68] Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products, OJ L 91, 9.4.2005, pp. 13–19.

[69] 10.10.2019 C(2019) 7140 final, https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/atmp_guidelines_en.pdf.

distribution and cession of tissues and cells, their derivatives and 'preparations' of cell therapy, if it has been authorised by ANSM.[70]

The clinical trials of ATMPs are considered interventional studies involving the human person in accordance with article L1121-1 of the French Public Health Code. Thus, the clinical trials authorisation procedure for ATMPs requires the prior authorisation of ANSM as well as the positive opinion of an ethics committee ('Comité de Protection des Personnes'). In accordance with EU law, two specific rules apply to investigational ATMPs given the difficulties linked to the assessment of these products. First, the time limit for the evaluation of the clinical trials application is extended. While it is 60 days for conventional medicines, it is 90 days for cell therapy and gene therapy medicinal products with the possibility of 90 supplementary days in case additional information or consultation of a specific group is required. There is no specific time limit in case of xenogeneic cell therapy medicinal products. Second, an explicit written authorisation from the national competent authority, i.e. ANSM, is required for clinical trials of investigational ATMPs as well as any medicine containing genetically modified organisms.[71]

Regarding the positive opinion of the Comité de Protection des Personnes, the relevant committee is chosen randomly and has between 45 and 60 days to give an opinion on clinical trials of investigational ATMPs.

In case of clinical trials of gene therapy products, the High Council of Biotechnologies is involved and has to provide two opinions. On the one hand, an opinion has to be requested by the future clinical trial applicant regarding the classification of the gene therapy product and containment measures for its handling. On the other hand, an opinion is requested by ANSM at the time of the evaluation of clinical trials application (authorisation of sites involved in clinical trials and duration of containment measures for patients after application of the gene therapy product).

Moreover, a new EU regulation on clinical trials has been adopted.[72] It allows the manufacturer to apply for a clinical trial authorisation via a single EU portal (common assessment for Part I on the scientific aspects-medicine documentation, and separate assessments by the concerned EU member state for part II on ethical aspects). The clinical trial has to be authorised within 60 days, i.e. 10 days for the validation of the application, 45 days for the evaluation and 5 days for the decision. For this purpose, a single decision by the concerned member state is notified to the sponsor through the EU Portal[73] after approval by a research ethics committee.[74] The new regulation will be applicable once technical matters will have been settled:

[70] Article R. 4211-53 of the French Public Health Code.

[71] Article 9 of Directive 2001/20/EC.

[72] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, pp. 1–76.

[73] Articles 5 to 8 of Regulation (EU) No 536/2014.

[74] Article 4 of Regulation (EU) No 536/2014 on the ethical review committee.

the full functionality of an EU portal and of the EU database on clinical trials.[75] Given that the European Commission has published a Decision on 13 July 2021 providing that "[t]he EU portal and the EU database have achieved full functionality and meet the functional specifications" in compliance with Regulation n¯536/2014,[76] this Regulation will apply from 31 January 2022.[77] For ATMPs, the specificities of the current clinical trial authorisation procedure will disappear almost entirely. The only specificities will relate to the possible additional time limit of 50 days for the purpose of consulting with experts on the evaluation of Part I on scientific aspects leading to a maximum of 110 days for the clinical trials of ATMPs to be authorised.[78] Nevertheless, clinical trials for which the request for authorisation is submitted before 31 January 2022 will continue to be regulated by Clinical Trials Directive 2001/20/EC until 31 January 2025.[79] Clinical trials for which the request for authorisation will be submitted between 31 January 2022 and 31 January 2023 can still be started in accordance with Articles 6, 7 and 9 of Clinical Trials Directive 2001/20/EC. In that latter case, Clinical Trials Directive 2001/20/EC will continue to apply until 31 January 2025.[80]

Finally, it should be highlighted that ANSM has established fast track procedures for the authorisation of clinical trials to be more reactive in regard to the future application of the European Regulation n°536/2014 on clinical trials.[81] Among these procedures, Fast track 1, which covers clinical trials of innovative treatments, is applicable to clinical trials of ATMPs in France from 18 February 2019 onward. It provides a maximum of 40 days for the assessment of clinical trials applications instead of the traditional time limit of 60 days.

[75] Regulation (EU) No 536/2014 and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, pp. 1–76.

[76] Commission Decision (EU) 2021/1240 of 13 July 2021 on the compliance of the EU portal and the EU database for clinical trials of medicinal products for human use with the requirements referred to in Article 82(2) of Regulation (EU) No 536/2014 of the European Parliament and of the Council, OJ L 275, 31.7.2021, pp. 1–2.

[77] Commission Decision (EU) 2021/1240 of 13 July 2021 on the compliance of the EU portal and the EU database for clinical trials of medicinal products for human use with the requirements referred to in Article 82(2) of Regulation (EU) No 536/2014 of the European Parliament and of the Council, OJ L 275, 31.7.2021, pp. 1–2.

[78] Article 6 § 7 of regulation (EU) No 536/2014.

[79] Article 98(1) of Regulation (EU) No 536/2014.

[80] Article 98(2) of Regulation (EU) No 536/2014.

[81] Regulation (EU) No 536/2014, OJ L 158/ 1–76.

4.3.4 *If the Product Is Not Classified as an ATMP, the Regulatory Pathway Applicable to Tissues and Cells May Apply*

Although it is unlikely that genome-edited iPS cells fall into this category, French Law has a special legal category called "cell therapy preparations" which are not ATMPs,[82] i.e. there is no substantial manipulation of the cells and the use of the cells is homologous as regards donor and recipient. During the process of revision of the French bioethics law, the study on the impact of the revision highlighted that the genetic modification of cells shall be considered as a substantial manipulation prohibiting the classification as "cell therapy preparation". Nevertheless, the adopted law itself does not change the current definition, but provides for the Government to adopt an ordinance within one year following the enactment of the Bioethics law to exclude substantially modified cells from the definition.

In France, cell therapy preparations are not medicines. They are governed by the legislation on tissues and cells. Health establishments have to be authorised by the Regional Agency for Health on the basis of an opinion by the Biomedicine Agency for the procurement of the cells for therapeutic uses.[83] Their preparation, storage, distribution, and cession for autologous or allogeneic therapeutic uses have to be carried out in establishments authorised by ANSM following an opinion by the Biomedicine Agency.[84]

4.4 Treatment of the Patient's Biological Data

In France, as in any other EU Member State, patients' biological data are mainly protected by Regulation (EU) n° 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (the so-called "GDPR")[85] as well as by Article 8 of the EU Charter of Fundamental Rights that explicitly aims at the protection of personal data. In the European Convention on Human Rights that has been ratified by France in 1974, Article 8 guarantees the right to respect for private and family life. The protection of personal data, including health and biological data, is also regulated in French law since 1978, France being one of the first countries in the world to get interested in the protection of personal data. The law n° 78-17 on information

[82] Mahalatchimy et al. (2011).

[83] Article L1242-1 of the French Public Health Code.

[84] Article L1243-2 of the French Public Health Code.

[85] OJ L 119, 4.5.2016, pp. 1–88.

technology, files and freedoms[86] has been revised several times, it was last amended by the law n° 2018-493 on personal data protection[87] in order to adapt it to the GDPR.[88]

There is no constitutional right on the protection of personal data as such. However, the 'Conseil Constitutionnel' which is the court controlling the conformity of French law with the French Constitution, held that personal data is protected under the right to respect for private life.[89] In the French Civil Code, the right to respect for private life is established in Article 9. Nevertheless, the French Public Health Code goes further in protecting explicitly the right to respect for private life as well as the confidentiality of personal data of any person entering the French health system.[90] The National Commission on information technology and freedoms (Commission nationale de l'informatique et des libertés (CNIL)) is in charge of ensuring the protection of personal data.

Data protection law is applicable to the genome editing of iPS cells with regard to the protection of personal data as well as the protection of health data, and eventually genetic data, which is particularly protected in EU and French laws as these data are considered sensitive data. For instance, in the context of scientific research, a data protection officer shall be designated, a data protection impact assessment should be carried out, and participants' rights shall be respected.[91]

More specifically, the CNIL shall be consulted for the processing of health data as defined by the GDPR, with a view to the requirement of either an authorisation or a notification regarding the processing of health data for research or the processing of such data aiming at a public interest such as ensuring high quality and safety standards for medicines.[92] The distinction between notification and authorisation depends on whether so called 'guidelines of references' established by CNIL exist. In case of the existence of such guidelines, a notification of conformity with these references will be sufficient. Consequently, CNIL is involved in the process of authorisation of investigational ATMPs and MTI-PP as well as in the national regulatory pathways for authorizing ATMPs not manufactured at an industrial scale (i.e. under the hospital exemption pathway (MTI-PP) and compassionate use schemes). Given the novelty and specificities of genome editing of iPS cells, there

[86] Loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés, JORF du 7 janvier 1978 page 227.

[87] Loi n° 2018-493 du 20 juin 2018 relative à la protection des données personnelles, JORF n°0141 du 21 juin 2018 texte n° 1.

[88] It has also been completed by the recent Décret n° 2018-687 du 1er août 2018 pris pour l'application de la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés, modifiée par la loi n° 2018-493 du 20 juin 2018 relative à la protection des données personnelles, JORF n°0177 du 3 août 2018 texte n° 12.

[89] Bachert-Peretti (2019).

[90] Article L1110-4 of the French public health code.

[91] Chassang (2017), p. 709.

[92] Commission Nationale de l'Informatique et des Libertés (2020).

are no guidelines of references from CNIL on this topic. It is, therefore, likely that an authorisation instead of a notification will be required.

4.5 Reform Efforts

Until 2021, the French regulatory regime was not fully suitable for gene therapy on the basis of human iPS cells to be differentiated into somatic cells for autologous re-transplantation, especially as it did not take into account the ethical and legal questions raised by iPS cells. In particular, French law was quite restrictive with a view to the embryo. However, it did not directly consider the possibility of differentiation of iPS cells into gametes or their aggregation with progenitor cells from extra-embryonic tissues to create entities similar to embryos although it was explicitly prohibited to create human embryos in vitro or by cloning for research purposes (see below Sect. 4.6). However, the last revision of the French Bioethics law adopted on 2 August 2021 after more than two years of debates in the French Parliament and beyond has provided major changes to the regulation of iPS cells as well as many other relevant issues.

Regarding human iPS cells, two modifications have been essential. First, human iPS cells are now legally defined within the Public Health Code as "cells which do not originate from an embryo and which are able to multiply indefinitely as well as to differentiate into all the types of cells that make up the organism".[93] Second, research protocols on iPS cells with the aim of differentiation of germ cells, obtaining in vitro embryonic development models, or insertion of iPS cells into an animal embryo for the purpose of its transfer to the female have to be notified to the Biomedicine Agency prior to the start of the research. Such a procedure enables the Director of the Agency after a public opinion of the higher organ of the Biomedicine Agency (the so-called 'conseil d'orientation'), to prohibit this kind of research if it does not meet ethical principles as well as applicable legal requirements as provided by the Civil Code and the Public Health Code. In the absence of opposition from the Biomedicine Agency within a time limit which will be set by forthcoming regulation, the research can start. Regarding research protocols on human iPS cells with other aims than those specifically mentioned above, the general legal frameworks for somatic cells are applicable (See above Sect. 4.2.2). Consequently, the Biomedicine Agency will have data on the use of CRISPR or other genome editing techniques in human iPS cells for research in France as long as it covers the most sensitive aims above-mentioned as specifically regulated by French Law.

Moreover, the new French bioethics law includes particular provisions on potential modifications of the genome of embryos. On the one hand, regarding the general prohibition of interventions into the human genome that alter the descent of persons,

[93] Article L. 2151-7.-I of the Public Health Code.

only research aiming at preventing and treating genetic diseases were not prohibited. This possibility has been extended to research on the prevention and treatment of diseases other than genetic diseases and to research for diagnostics purposes. The higher administrative French Court, the Conseil d'Etat, which has notably the role of advising the Government on legislative proposals, has considered such an extension to be valid with regard to article 13 of the Oviedo Convention providing similar exceptions to the general prohibition of interventions into the human genome (see below Sect. 4.6).[94] On the other hand, the previous prohibition of creating embryos for research has been limited. First, the prohibition of the "conception of in vitro human embryos" and of the "constitution by cloning of human embryos" for research purposes has become the prohibition of "conception of in vitro human embryos by gamete fusion", while the part on cloning of human embryos has remained unchanged. Second, the prohibition of "creating transgenic or chimeric embryos" has been restricted to the prohibition of the "modification of a human embryo by adding cells from other species". One can welcome this necessary clarification of the legal prohibition to create chimeric embryos by specifying that it concerns the "adding of cells from other species" to human embryos. It should be highlighted that there is no prohibition regarding the addition of human cells (notably pluripotent cells) to animal embryos, such researches have to be notified to the Biomedicine Agency. Most importantly, it is now possible to modify the genome of human embryos for fundamental research purposes, to be destroyed later on, in limited cases of basic research authorised by the Biomedicine Agency. The rationale behind this change is that the previous legal prohibition was irrelevant as it allowed some techniques of genome editing such as inactivation of a gene but prohibited other techniques involving the introduction of new genes while both raised the same ethical questions. Other legal changes complete the legal framework of what can be done or not in research, especially regarding human embryos.

Since researchers have shown in 2016 (i.e. after the last revision of the bioethics law which occurred in 2011) that embryos can be cultured in vitro for more than 7 days, the new Bioethics Law establishes a legal time limit of 14 days for the culture of embryos for research purposes.

Moreover, the legal possibility to stop storage of supernumerary embryos donated for research if they have not been used for research for 5 years after consent to donation has also been established.

Finally, even though the genome editing of iPS cells should not cover embryonic stem cells, it needs to be highlighted that the new Bioethics Law provides more permissive regulation regarding research on embryonic stem cells. This is especially notable taking into account that research on embryonic stem cells was fully prohibited in the first French bioethics laws of 1994. It was then prohibited in principle but exceptions were allowed under the 2004 and 2011 revisions of the bioethics law. It, finally, became permissible through Law n°2013-715 modifying the bioethics law which enabled research on human embryos and embryonic stem

[94] Conseil d'Etat (2019), p. 24.

cells under specific conditions.[95] In particular, such research shall be authorised by the Biomedicine Agency only if it was conducted on supernumerary embryos, scientifically relevant, and for medical purposes, and if it respected ethical principles, and if the research could not be done without using embryos or human embryonic stem cells according to the state of the art. Moreover, the required consent of parents, which ends parental custody over the supernumerary embryos, was strengthened: after the couple is supplied with information, consent shall be given in writing and had to be confirmed after expiry of a 3 months period of reflection. The consent can also be revoked by either of the two parents without need to give any reasons as long as research has not started.[96] The new Bioethics Law goes a step further as it introduces a distinction between research on embryos and research on embryonic stem cells. For research on human embryos, the legal regime of authorisation is maintained under the same strict conditions although the research can now be done with the aim to improve knowledge of human biology and not only for medical purposes. However, for research on human embryonic stem cells, the regime has changed from an authorisation to a notification scheme. Accordingly, the research can start, if there is no decision to the contrary by the Biomedicine Agency. Consequently, in this case, there is no more need for the research team to prove, on the basis of the state of the art, that there is no alternative to the use of embryonic stem cells. Thus, the new Bioethics Law is more permissive regarding the legal regimes applicable to the research on human embryonic stem cells, and to the modification of the genome of human embryos subject to specific conditions: the subsequent destruction of the research embryos after 14 days of culture and the authorisation of the research by the Biomedicine Agency.

4.6 Outlook: Human Germ Line Intervention Through Genome Editing

In France, Article 16-4 of the civil code provides: "No one may infringe upon the integrity of mankind. Any eugenic practice which aims at organizing the selection of persons is forbidden. Any medical procedure whose purpose is to cause the birth of a child genetically identical to another person alive or dead is forbidden. Without prejudice to any research that aims at preventing, diagnosing and treating diseases, there may be no transformation of genes in order to alter the descent of a person." This provision consequently includes the possibility of germ line interventions, including through genome editing in human beings, for research aiming at preventing or treating genetic diseases. This exception to the general principle of prohibition of human genome interventions altering the descent of a person has

[95] Loi n° 2013-715 du 6 août 2013 tendant à modifier la loi n° 2011-814 du 7 juillet 2011 relative à la bioéthique en autorisant sous certaines conditions la recherche sur l'embryon et les cellules souches embryonnaires, JORF n°0182 du 7 août 2013 page 13449 texte n° 1.

[96] Article L. 2151-5 of the French Public Health Code.

already been included in the first bioethics laws of 1994. Although the government's legislative proposal of 1994 was to prohibit any modification of the germline, Parliament amended the draft to avoid restrictions of gene therapy research.[97]

Consequently, the following activities are allowed under specific conditions in France as long as the embryo is not considered a legal person by French law but only a 'potential human person': medically assisted reproduction to avoid the transmission of a particularly severe disease to the child,[98] prenatal or preimplantation diagnosis to detect a severe disease,[99] or research on embryos.[100]

Moreover, as said above in Sect. 4.5, the new bioethics law has extended the possibility of human genome interventions altering the descent of a person to research on the prevention and treatment of diseases other than genetic diseases and for diagnostic purposes. In that context, France has signed and ratified, thanks to the 2011 bioethics law, the Oviedo Convention. Thus, article 13 of the Oviedo Convention is applicable in France. It states that "[a]n intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants." Interestingly, the French Conseil d'Etat held that extending the possibility of human genome interventions altering the descent of a person to research on the prevention and treatment of diseases does not contravene Article 13 the Oviedo Convention. However, the reasoning underlying French law and the Oviedo Convention seems to be in conflict. Indeed, French law allows human genome interventions altering the descent of a person only for research that aims at preventing, diagnosing and treating diseases. On the contrary, the Oviedo Convention allows human genome interventions for preventive, diagnostic or therapeutic purposes, however only if they do not aim to alter the descent of person. However, it seems to be implied that they could have the effect of altering the descent of a person as long as it is not their primary aim. Hopefully, clarifications should rapidly come from the drafting group established by the Committee on Bioethics of the Council of Europe in order to "provide clarifications on the terms 'preventive, diagnostic and therapeutic'" and to "avoid misinterpretation of the applicability of this provision to 'research'."[101]

Finally, as discussed above in Sect. 4.5, the new Bioethics Law has allowed the genome editing of human embryos in fundamental research. Nevertheless, genome editing of human embryos for other purposes than fundamental research (with the time limit of 14 days) remains prohibited as it is clearly stated both in the context of

[97] At the time, the Senate even proposed to include an explicit authorisation of research aiming to eradicate genetic diseases. The National Assembly rejected this amendment as the eradication of genetic diseases implies genetic selection and is not feasible either because mutations always occur in genetics. That is why "eradication of genetic diseases" has been replaced by "preventing or treating genetic diseases". See notably: Vacarie and Goré (1994), p. 613.

[98] Article L2141-2 of the French Public Health Code.

[99] Article L2131-1 and following of the French Public Health Code.

[100] Article L2141-8 of the French Public Health Code.

[101] Council of Europe, Committee on Bioethics, 18th meeting, 1–4 June 2021, DH-BIO/Abr RAP18.

Assisted Reproductive Technology and in clinical trials. For the former, "no intervention aimed at modifying the genome of the gametes or the embryo can be undertaken".[102] For the latter, Article 90 of Regulation (EU) 536/2014, which maintains a previous provision of Directive 2001/20/EC, prohibits to carry out "gene therapy clinical trials which result in modifications to the subject's germ line genetic identity". This provision applies directly in France as in every other Member States of the European Union.[103]

4.7 Conclusion

The French regulation of genome editing of human iPS cells relies on a complicated legal framework with several regulatory pathways. Nevertheless, it has been highly clarified by the last revision of the French bioethics law which mainly provides a legal definition of human iPS cells, clarifies the regulatory pathways for human iPS cells, and allows genome editing of human embryos for fundamental research purposes while maintaining safeguards. Hence some gaps have been closed, such as regulatory oversight of research on iPS cells by the Biomedicine Agency. Overall, there is no general trend towards de-regulation in France. Nevertheless, regulatory restrictions have been alleviated in order to allow genome editing of iPS cells to unfold its therapeutic potential.

Acknowledgement This work has been supported by ANR-funded I-BioLex project (ANR-20-CE26-0007-01, coord. A. Mahalatchimy).

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[102] Article L. 2141-3-1 of the Public Health Code.

[103] Article L. 2141-3-1 of the Public Health Code.

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Chapter 5
Regulation of Genome Editing in Human iPS Cells: Switzerland

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Abstract In Switzerland, gene/cell therapies using genome edited iPSCs for somatic differentiation are generally permitted. Although Swiss Law does not contain specific regulations regarding iPSCs or genome editing in human cells, several norms apply. According to the Transplantation Ordinance, human iPSCs, as well as any gene/cell therapy using them, qualify as transplant products. Therefore, their handling needs to be authorised as described in the present contribution. Whenever genome edited iPSCs are used for somatic differentiation, this work argues that their differentiation into gamete cells is currently not permitted as it is, at present, highly possible that their creation may lead to unintended genetic modifications. Swiss Law, however, strictly prohibits genetic modification of germ cells or embryos (including their precursor cells)—this work presents the effect of this prohibition on different forms of germ line interventions. As all such procedures require personal data, Swiss data protection requirements are analysed. Genetic data qualifies as sensitive data that calls for a higher level of protection. Despite the fact that several norms apply to questions of iPSCs and genome editing, de lege lata a clear regulation and suitable definitions for the current state of research are missing. The present contribution favours an inclusion of, among others, iPSCs in existing definitions and aims to fuel the discussion on a specific research privilege for genome editing and artificial gametes subject to strict limitations.

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H.-G. Dederer, G. Frenken (eds.), *Regulation of Genome Editing in Human iPS Cells*, https://doi.org/10.1007/978-3-030-93023-3_5

5.1 Introduction

5.1.1 Genome Editing in Human Cells

The present contribution examines the current regulatory framework and the requirements applicable to genome editing in human cells in Switzerland. The focus hereby lies on human induced pluripotent stem cells (human iPS Cells, human iPSCs) and their somatic differentiation for use in gene/cell therapy. However, their use in germ line interventions will also be analysed. One should not forget that a great deal of research still involves embryonic stem cells (ESCs), which can play a role not least in germ line interventions. Also, because Switzerland has a specific research law regarding ESCs, this type of cell will also be discussed below.

Before turning to the legal aspects, however, a short biotechnological introduction seems appropriate. Induced pluripotent stem cells (iPSCs) are pluripotent[1] stem cells created by reprogramming non-pluripotent somatic cells.[2] The conversion is triggered by the externally activated expression of special genes (transcription factors) in the somatic cell, for which various techniques exist. Although iPSCs and embryonic stem cells (ESCs) share remarkable similarities (e.g. high self-renewal rate, similar morphologies and growth properties),[3] several studies claim that there are differences in the functioning[4] and thus conflicting conclusions regarding the similarities between human iPSCs and ESCs exist.[5] Despite these uncertainties, human iPSCs have a high medical potential, as research on them involves fewer ethical problems than research on embryonic stem cells. In addition, human iPSCs, that are specially adapted to patients, can be generated. IPS Cells have thus revolutionised the field of biomedical research and are very promising for the future.[6]

In cell therapy, the transplanted cells can come from the patient or from a donor, depending on the application. They are intended to repair, replace or support patient cells or tissue after transplantation.[7] In gene therapy, functional genes are introduced into cells to replace missing or defective genes and thus compensate for genetic disorders. Human iPSCs may be used in both therapies, as well as in a combination

[1] Pluripotency describes the ability of cells to differentiate into several (in latin *plures* = *several*) cell types (cf. Denker 2002, p. 21).

[2] EuroStemCell (2016); cf. Cantz (2022), Chap. 2, Sect. 2.1 (this volume).

[3] Yamanaka (2012), pp. 680 et seq.

[4] Yamanaka (2012), p. 680 with reference to e.g. Chin et al. (2009), Ghosh et al. (2010) and Deng et al. (2009).

[5] Yamanaka (2012), p. 680 with reference to studies that concluded that the distinction is difficult to establish, e.g. Guenther et al. (2010), Newman and Cooper (2010) and Bock et al. (2011).

[6] Mandip and Steer Clifford (2019); Yu et al. (2021).

[7] E.g. chimeric antigen receptor tumor cells (also known as CAR T cells) are T-cells that have been genetically engineered to produce an artificial T-cell receptor for use in immunotherapy (cf. Jensen et al. 2019).

of both. Regarding the latter, methods such as the CRISPR/Cas9 technology can be used. CRISPR/Cas9 is a "genome-scissor" used to remove defective genomes with a precision hitherto unknown, and in a highly cost-effective way, after the reprogramming of somatic[8] cells to correct defective human iPSCs[9] and subsequently to differentiate them in specific cell types for cell replacement.[10] Possible fields of application include the development of therapeutic products based on iPSCs, such as for the treatment of Parkinson's disease or amyotrophic lateral sclerosis (ALS). Furthermore, human iPSCs can be an important factor in regenerative medicine, for the purpose of replacing or regenerating damaged cells, organs or tissues in order to restore normal functions. IPSCs in combination with their genetic identity specific to patients, opens up the possibility of autologous transplantation, e.g. in the field of ophthalmology.[11] Apart from that, genome-edited human iPSCs might be used for enhancement purposes, i.e. to improve performance rather than to treat an existing disease.

5.1.2 Research on Gene/Cell Therapies in Switzerland

According to the Swiss Federal Office of Public Health (FOPH) the origins of the legal basis on research on embryonic stem cells (ESCs) dates back to 2001, when, on 28 September, the Swiss National Science Foundation (SNSF) decided to fund a research project involving imported human embryonal stem cells.[12] During the past years, several interesting projects have been concluded. For an overview, see the website of the FOPH[13] which publishes a list of current research projects, especially those using ESCs and stem cell lines. Further information and insights into research projects in Switzerland are provided by the Swiss Stem Cell Network (SSCN) and its affiliated organisations, the Neuroscience Network Basel (NNB), the Basel Stem Cell Network (BSCN) and the Stem Cell Research Platform Berne. Besides that, Prof. Dr. Marisa Jaconi, based in Geneva, maintains, together with hospitals, a worldwide register of stem cell lines. Below are some examples of past and recent research projects on stem cells:

In 2002/2003 the TA-Swiss, the Centre for Technology Assessment at the Swiss Science and Technology Council in Berne conducted a first study on human stem cells and its ethical considerations, in which they examined the embryo research bill

[8] For more details cf. Hockemeyer and Jaenisch (2016); Wilbie, Walther and Mastrobattista (2019).

[9] See e.g. Kang et al. (2016).

[10] Cf. disease modelling of Parkinson patients by the research group headed by Hans Schöler, Max Plank Institut for Molecular Biomedicine, and Thomas Gasser, Hertie-Institut for Clinical Neuroscience.

[11] Pane et al. (2016), Chapter 3.6.

[12] Federal Office of Public Health (2018a).

[13] Federal Office of Public Health (2018c).

of November 2002 and called for a broader discussion.[14] In 2008, Prof. Jaconi and her research group derived the first Swiss human embryonic stem cell line from a single blastomere of an arrested four-cell stage embryo.[15] In 2017, the National Research Programme No. 63, "Stem Cells and Regenerative Medicine", was completed. It aimed at boosting basic research on stem cells and regenerative medicine and at encouraging top scientists with an excellent track record in developmental and cell biology to engage in this field. Moreover, it aspired to recruit and train young scientists in this field by providing specific scholarships.[16] Between 2010 and 2015, 12 groups from Basel, Berne, Geneva, Lausanne and Zurich worked in this research area, with a budget of 10 million Swiss francs.[17] One of the projects was led by Heinrich Reichert (Basel) and Jürgen Knoblich (Vienna).[18] They investigated the issue of uncontrolled stem cells causing tumours. The researchers advise against using stem cells or intermediate cells directly for regenerative medicine because the risk that these cells trigger tumours is unpredictable. They concluded that, for the time being, only fully differentiated cells should be considered for use in regenerative medicine.

As everywhere else, genome editing of human iPS Cells has, of course, been practiced for several years in Switzerland. The first human iPS Cells were developed in Switzerland in 2007 (Yamanaka Protocol). Several projects have been carried out since that time, including the following which are mentioned by way of illustration: In 2016, the lab of Matthias Lutolf at the École Polytechnique Fédérale de Lausanne (EPFL) developed a 3D gel that promotes the ability of cells to reprogramme into stem cells by "squeezing" them into shape, promising a more effective way to generate iPS Cells.[19] At the University of Zurich, the research group around Prof. Dr. Edna Grünblatt is using iPSC from hair follicles to study neurodevelopmental disorders such as Attention-deficit/hyperactivity disorder (ADHD).[20] According to the stem cell register kept by Prof. Jaconi, there are six iPS Cell lines listed in Switzerland at this moment in time, all of them based at the Swiss Institute of Technology in Lausanne.[21]

Switzerland is a unique location for the pharmaceutical industry and thus, besides diverse academic research projects, or in cooperation with them, there are numerous industry activities. For instance, Roche conducts stem cell research in-house and in cooperation with external partners, aiming to develop treatment strategies for

[14] Hüsing et al. (2003).

[15] Cf. Feki et al. (2008).

[16] Swiss National Science Foundation (2016).

[17] For an overview of the research projects see Swiss National Science Foundation (2015).

[18] Another fascinating project by Knoblich includes genetically engineered cerebral organoids (Bian et al. 2018, pp. 631–639).

[19] Caiazzo et al. (2016).

[20] Cf. Re et al. (2018).

[21] Find stem cell research via https://hpscreg.eu/search?q=human iPSCs, search result for "human iPSCs".

incurable or inadequately treated severe diseases.[22] Their research projects include the use of stem cell research as a discovery tool, as well as projects looking into potential therapeutic modalities.[23] Novartis is inter alia focussed on gene therapies for patients and families afflicted with rare and life-threatening neurological diseases. As another example, Novartis grew human neurons from human iPSCs derived from skin cells in 2015 to coax human iPSCs to differentiate into cortical excitatory neurons, e.g. relevant to Alzheimer. In doing so, the team scaled up protocols developed in academic labs to facilitate drug discovery in neuroscience.[24]

5.1.3 Overview

Against this background, this contribution presents the existing regulatory framework—focusing on human iPSCs—including the corresponding national and international norms (Sect. 5.2.1) and introducing the responsible regulatory authorities (Sect. 5.2.2). Section 5.3 will focus on the regulatory prerequisites for gene/cell therapy using genome edited human iPSCs for somatic differentiation. In doing so, necessary product development steps such as clinical trial (Sect. 5.3.1), market placement (Sect. 5.3.2) and further market-related activities (Sects. 5.3.3 and 5.3.4) will be examined. After focusing on the somatic application, Sect. 5.4 aims to open the discussion around germ line interventions, including interventions on embryos, germ cells and stem cells. As to the latter, this work sheds light on the subject of artificial gametes.[25] Given that in all of the processes involved biological material and genetic data is of major importance, Sect. 5.5 will look at the state of regulation on the protection of personal health data in Switzerland. The conclusion (Sect. 5.6) will summarise the main arguments and reform efforts stipulated in the previous analyses.

5.2 Genome Editing of Human iPS Cells: An Overview of the Regulatory Framework

Human iPS Cells are neither explicitly defined, nor explicitly regulated in Swiss law.[26] Of course, this does not mean that iPS Cells are not regulated; on the contrary, a variety of norms are relevant. In order to provide a valuable overview of this

[22] Roche (2020), p. 2.

[23] Roche (2020), p. 3.

[24] Cf. Kneller (2015).

[25] "Artificial gametes" hereinafter mean gamete cells derived from human IPSCs in vitro (Cf. Cantz (2022), Chap. 2, Sect. 2.3, this volume).

[26] Sprecher (2020), pp. 288 et seq.

regulatory framework, it should be approached from a broader viewpoint, including comparisons with other areas of regulation—this shall be set out below. Section 5.2.1.1 will focus on the norms enshrined in the Swiss Federal Constitution (FedCst), including their historical development, and the specifying national laws and ordinances that provide a definition of human iPSCs, as well as directly applicable international rules (Sect. 5.2.1.2). After that, the regulatory authorities will be presented in Sect. 5.2.2.

5.2.1 Regulatory Framework

5.2.1.1 The National Framework

5.2.1.1.1 Fundamental Rights in the Swiss Constitution

In general, in Switzerland, there is no self-contained "health constitution" or chapter dealing with health questions in the Federal Constitution.[27] However, the fundamental framework includes various articles that address different aspects of health law. Already prior to creating specific norms (below), and prior to any work involving genetic modifications, the constitution incorporated fundamental rights that provide certain values.

From the patient's perspective, human dignity[28] is the central starting point for the unconditional protection of fundamental rights of all humans.[29] Compared to more specific fundamental rights, Art. 7 FedCst is a catchall fundamental right, which encompasses the ultimately incomprehensible human being. An offence against human dignity would e.g. be committed if embryos were genetically modified in the interest of parents or society. Less obviously linked to health law is the equality of rights in Art. 8 FedCst. This fundamental right is important because the majority of medical services are provided by public authorities and thus the right to equal access to such care is relevant. The core of the debate on fundamental rights in the health sector is the right to life and personal freedom, enshrined in Art. 10 FedCst.[30] Para. 1, the right to life, is the existential basis of the right to physical and psychological integrity, enshrined in para. 2 of Art. 10 FedCst.

[27] Gächter and Rütsche (2018), par. 77; Dupont (2020), p. 2112, par. 58 et seq.

[28] Further see Raposo (2019b), pp. 249–257. Raposo elaborates on the concept of human dignity and the effect of gene editing, arguing She states that criticism of genome editing cannot be based on the argument of human dignity.

[29] Cf. Belser and Molinari (2015a), par. 46.

[30] Gächter and Rütsche (2018), par. 161.

Ultimately, the right of sick people to necessary and adequate medical care derives from this, or at least in conjunction with it, as per Art. 41 para. 1 lit. b FedCst.[31]

All interferences with the human body, including medical interventions, fall under this protection. Thereby, an interference does not necessarily depend on physical pain. Even nascent life—despite detailed discussions—enjoys the right to physical integrity.[32] Although the Federal Supreme Court has not yet taken a clear stand on the issue, but only casually mentioned the rights of the embryo,[33] human life must be respected independently of timing. As such, the embryo enjoys its own special, albeit limited, fundamental rights protection.[34] At the same time, effective protection increases from conception to birth, as from when there must be full protection.[35] A distinction must be made between minor and major interferences, with major interventions always requiring a legal basis.[36] Whereas, for example, compulsory drug treatment is considered to be a serious intervention,[37] blood sampling, for example, is considered as a minor intervention in physical integrity.[38] It should be noted, however, that even a slight interference with the right to physical and mental integrity (such as a medical examination) is unacceptable, if it is carried out without the consent of the person concerned, even if the conditions of Art. 36 FedCst (further below) are fulfilled.[39] Moreover, the Federal Supreme Court ruled early on that the desire to have children is a fundamental manifestation of personal development and subsumed it under Art. 10 para. 2 FedCst.[40] In

[31] Schweizer (2014); BGE 145 V 97 cons. 8, 101 et seq.; 145 v 116 cons. 6.3, 127; 142 V 58 cons. 5, 64 et seq.; 138 II 513 cons. 8.4, 523; 130 I 16 cons. 5.2, 20; European Court of Human Rights (ECtHR) Reynolds v. Royaume-Uni, 2694/08 [2012], para. 60 et seq.; Panaitescu v. Roumanie, 30909/06 [2012], para. 30; Dodov v. Bulgarie, 59548/00 [2008], points 80 et seq.; Tarariyeva v. Russie, 4353/03 [2006], para. 73–88; Mehmet Sentürk and Bekir Sentürk v. Turquie, 13423/09 [2013], No. 81; Arskaya v. Ukraine, 45076/05 [2013], No. 63; Bajic v. Croatie, 41108/10 [2012], para. 87 et seq., according to which Art. 2 ECHR implies a positive obligation of the state to create a legal regulation that forces public and private hospitals to take appropriate measures to protect patients; cf. comm. on Art. 41, para. 39 et seq.

[32] Hertig Randall and Marquis (2021), Art. 10 para. 15 FedCst.; Tschentscher (n.d.), par. 11; Schweizer (2014), par. 10, 23; Rütsche (2009), pp. 230 et seqq.; Steinauer and Fountoulakis (2014), pp. 434 et seqq.

[33] BGE 119 Ia 460, 502 cons. 12e (translated): “Dignity of the human being, which already belongs to the embryo in vitro”.

[34] For more information regarding the protection of embryos and foetuses see Savioz-Viaccoz (2021); Tschentscher (n.d.), par. 11; Schweizer (2014), par. 10, 23; Schweizer (2002), pp. 41 et seqq., especially pp. 56 et seq.; Rütsche (2009), pp. 230 et seqq.; Manaï (2013), pp. 348 et seqq.; cf. Manaï (2009).

[35] Tschentscher (n.d.), par. 11; see e.g. ECtHR Asiye Genç v. Turkey, 24109/07 [2015], para. 80.

[36] Art. 36 para. 1 FedCst.

[37] BGE 130 I 16, cons. 3; 130 I 65, E. 3.3, 68; 127 I 6, cons. 5g; 126 I 112, cons. 3a et seqq.; 115 et seq.

[38] BGE 124 I 80, cons. 2d, 82; 128 II 259 concerning cheeks-mucosa smear test.

[39] BGE 136 V 117, cons. 4.2.2.1, 126.

[40] BGE 115 Ia 234 (on the then St. Gallen Reproductive Medicine Act) and BGE 119 Ia 460 (on the then Basel Reproductive Medicine Act).

addition, Art. 12 FedCst sets out the right to assistance when in need, which entails a more general right to fundamental medical care, which in an emergency case cannot be denied.[41] In nearly all cases, medical treatment touches on the patient's private and intimate life. This sphere is protected by Art. 13 para. 1 FedCst in conjunction with Art. 8 para. 1 ECHR. As a result, the Federal Supreme Court derived, for instance, a right of access to medical records.[42] Furthermore, Art. 13 para. 2 in conjunction with para. 1 FedCst provides the basis for the right of personal health data protection, which is examined in greater detail below. Art. 15 FedCst ensures the freedom of belief and religion, which protects patients against any impairment, be it through medical treatment violating their beliefs.

Besides those fundamental rights of the patient, researchers or doctors, who apply genetic editing, may also claim certain fundamental rights. The handling of cells includes, inter alia, their collection, testing, preparation, import and export, storage and transplantation.[43] Analogous to the non-human sphere,[44] these acts represent scientific activities that are protected by the Swiss Federal Constitution: firstly, Art. 20 FedCst guarantees academic freedom for all natural persons—and depending on the objectives—for juridical persons, too.[45] Academic freedom entails the freedom of research, as well as the freedom to acquire knowledge, freedom of teaching and freedom of communicating in the field of science. More specifically, the freedom of research includes the choice of questions and methods, the planning and implementation of material collections, the determination of the state of research, the preparation of scientific reports, publications and summaries, as well as the critical analysis of the research results.[46] Limitations on the academic freedom derive, *inter alia,* from the fundamental right to protection of personality, granted by civil and criminal law, as well as by specific health related laws (which will be examined below).[47] Interestingly, the Federal Supreme Court declared a general ban on research on (unfertilised) germ cells to be constitutional.[48] Secondly, scientific activity is guaranteed by the principle of (individual) economic freedom in Art. 27 FedCst. The free choice of profession and free access to an activity enjoys special protection under private and public law.[49]

[41] BGE 146 IV 297 cons. 2.2, 303 et seq.; 131 I 166 cons. 8.2, 182; Amstutz (2002), pp. 212 et seq.; Gächter and Rütsche (2018), par. 168, concerning the emergency case see BGE 138 V 310 cons. 4, 315; Kanton Zürich § 38 Gesundheitsgesetz vom 2. April 2007: Beistands- und Aufnahmepflicht der Institutionen des Gesundheitswesens in dringenden Fällen.

[42] BGE 122 I 153, cons. 6b.

[43] E.g. Art. 2 para. 1 lit. a Transplantation Ordinance.

[44] Cf. Errass (2018), p. 117, who, carefully and highly informatively, elaborates on regulations of plant breeding methods.

[45] Schweizer (2020a), p. 365; Schweizer and Hafner (2014), par. 22; Gächter and Rütsche (2018), p. 178.

[46] Schweizer and Hafner (2014), par. 15; Müller and Schefer (2008), pp. 546 et seq.; Hertig Randall (2015), par. 5 et seqq.; above all BGE 127 I 145, 152 cons. 4.b.

[47] Biaggini (2017c), par. 14; Schweizer (2020a), p. 369.

[48] BGE 115 Ia 234, 169 et seqq.

[49] For further elaborations see, for instance, Vallender (2014) and Uhlmann (2015).

In general, restrictions on these basic constitutional rights may only be justified if in the public interest or for the protection of the fundamental rights of others (Art. 36 para. 2 FedCst). Hence, there can be a tension between the rights of the patient and the scientific freedom or the economic freedom of researchers, doctors or pharmacologists. In light of the principle of proportionality, a case-by-case analysis is required to evaluate the prevailing right.[50] Apart from these conflicting fundamental rights, the Constitution sets out several specific norms regarding health law. However, before addressing the specific norms, a review of the historical background seems to be of interest.

5.2.1.1.2 Historical Perspective on Constitutional Medical Regulation in Switzerland

Whilst heterologous insemination has been practiced in Switzerland since the sixties, it was not until the end of the eighties that Switzerland began to comprehensively regulate assisted or reproductive medicine and human and extra-human genetic engineering.[51]

The first guidelines on reproductive medicine and genetic engineering where established by Swiss doctors when, in 1981, the Swiss Academy of Medical Sciences (SAMS) published the first guidance on artificial insemination.[52] In 1985, guidelines for in vitro fertilisation and embryo transfer were adopted.[53] On 3 June 1993, the organisation issued guidelines on genetic testing on humans.[54] With the enactment of formal laws (see below), the SAMS withdrew the previous guidance. The standards issued by the SAMS do not represent binding law but recommendations. However, they do have a fundamental indirect legal effect, as they serve as inspiration for the creation of legally binding norms and provide assistance in applying the law.[55]

At an early stage, various cantons took legislative action in different ways and applied the SAMS guidelines differently.[56] Two decisions of the Swiss Federal Supreme Court in 1989 and 1993 provided the starting point for more centralised

[50] Schweizer (2014), pp. 39 and 56; cf. Häfelin et al. (2020), Chapter 1, § 9; Kiener et al. (2018), p. 125 with further remarks; Hottelier (2007), par. 43; Martin (2007), pp. 224 et seqq.; Federal Supreme Court (FSCt) 1C_74/2015 [02.02.2015], cons. 4.2; BGE 140 III 616 cons. 3.6.6, 633 et seq.; 132 I 181, cons. 4.5, 193 f.; 130 I 16, cons. 5, 19 ff.; 129 I 173, cons. 5.1, 181; 119 Ia 460; ECtHR Gillberg v. Sweden, 41723/06 [2012]. para. 82–97.

[51] Reusser and Schweizer (2014b), par. 1.

[52] SÄZ 1982, 623.

[53] SÄZ 1985, 1127.

[54] SÄZ 1993, 1449.

[55] Cf. Sprecher (2020).

[56] While one group of cantons only declared the SAMS guidelines to be applicable (AR, BL, GE, OW, TG and TI), other cantons created independent solutions (e.g. AG, NE), some of them very restrictive (BS, GL, SG).

regulation. They established a general ban on in-vitro fertilisation and decided that heterologous insemination is not compatible with the fundamental right of personal freedom.[57] In 1987, the Swiss population filed a popular initiative against abuses of reproductive and genetic engineering in humans.[58] Although the initiative was withdrawn, it boosted the adoption of Art. 24^{novies} FedCst[59] on 17 May 1992. In line with a more holistic view, this amendment encompassed both the human and non-human domain. This was changed in 1996, in the preliminary draft of a totally revised FedCst, when the former Art. 24^{novies} was surprisingly split into two articles: Art. 119 and 120 FedCst. Both articles call on the legislator to protect people from abuses of reproductive medicine and genetic engineering and to comply with the prohibitions, restrictions and guarantees of fundamental rights.[60] Irrespective of its international orientation, scientific research has of course been strongly influenced, nearly impaired, by this unexpected decision.

5.2.1.1.3 Current National Framework of Medical Regulation

The recent constitutional articles establish the basis for health protection (Art. 118), complementary medicine (Art. 118a), general rules for research on human beings (Art. 118b), reproductive medicine and gene technology involving human beings (Art. 119), transplant medicine (Art. 119a) and non-human gene technology (Art. 120). The most relevant norms for the purposes of the present contribution will be examined in more detail below.

Firstly, Art. 118 para. 1 FedCst contains the general mandate for the Confederation to take measures to protect human and animal health.

Art. 118 FedCst Health Protection

1. The Confederation shall, within the limits of its powers, take measures for the protection of health.
2. It shall legislate on:
   a. the use of foodstuffs as well as therapeutic products, narcotics, organisms, chemicals and items that may be dangerous to health;
   b. the combating of communicable, widespread or particularly dangerous human and animal diseases;
   c. protection against ionising radiation.

The protection mandate includes direct and indirect impairments of health, e.g. due to noise emissions. The main point here is that the Confederation has only limited, fragmentary competence under Art. 118, as the cantons have extensive

[57] BGE 115 Ia 234, BGE 119 Ia 460.

[58] BBl 1987 II 1208 ff. and Federal Council's Dispatch on this initiative BBl 1989 III 989 et seq.

[59] Former Federal Constitution of 1874, valid until the end of 1999.

[60] Reusser and Schweizer (2014b), par. 3.

responsibilities.[61] The actual legislative competence of the Confederation is defined in para. 2. It includes the handling of certain goods and objects (lit. a), certain diseases (lit. b) and protection against ionising radiation (lit. c). Based on Art. 118 FedCst, as well as on Art. 95 FedCst on the protection of professional activities in the private sector, is, among others, the Federal Act on Medicinal Products and Medical Devices (Therapeutics Products Act, TPA) of 15 December 2000. The TPA aims to protect human and animal health and to guarantee that only high quality, safe and effective therapeutic products are placed on the market (Art. 1 para. 1 TPA). It shall further protect consumers (Art. 1 para. 2 lit. a TPA), help to ensure that the products are used in accordance with their purpose and in moderation (Art. 1 para. 2 lit. b TPA) and help to secure a well-organised supply of therapeutic products and necessary information (Art. 1 para. 2 lit. c TPA). Generally applicable to therapeutic products, narcotics and therapeutic treatments relating to therapeutic products (Art. 2 TPA), Articles 3, 5–33, 58–67 and 84–90 apply *mutatis mutandis* to the handling of transplant products (Art. 49 Transplantation Act). The TPA was recently revised in January 2019. The amendments include facilitating market access for certain medicinal products (especially medicinal products approved in the EU or EFTA countries), improving medicinal product safety, improving integrity and transparency (introduction in 2020) and the new Council of Europe's Medicrime Convention.[62] Important changes are currently planned concerning medical devices (MD) in reaction to the new EU regulation on medical devices. These alignments are based on the Mutual Recognition Agreement (MRA) between Switzerland and the EU, which requires equivalence of the corresponding legal regulations. In order to provide a legal basis, the TPA, the Human Research Act (HRA) and related implementing ordinances will be partly revised. Originally expected for 2020, the revision is postponed due to the COVID-19 pandemic.[63]

Art. 118*b* FedCst grants the federal government comprehensive competence to regulate research on humans. Para. 2 of the article enshrines the principles applicable to research in biology and medicine involving human beings.

Art. 118*b* FedCst Research on Human Beings

1. The Confederation shall legislate on research on human beings where this is required in order to protect their dignity and privacy. In doing so, it shall preserve the freedom to conduct research and shall take account of the importance of research to health and society.
2. The Confederation shall adhere to the following principles in relation to biological and medical research involving human beings:

[61] Reusser and Schweizer (2014a), par. 2–6, see the same contribution for further details on Art. 118.

[62] Convention on the counterfeiting of medical products and similar crimes involving threats to the public health of 28 November 2011 (CETS no. 211), Ratified by Switzerland in 2018 (SR 0.812.41); Federal Office of Public Health (2020a).

[63] Federal Office of Public Health (2020b).

a. It is a requirement for any research project that the participants or their legal representatives have given their informed consent. The law may provide for exceptions. A refusal is binding in every case.
b. The risks and stress for the participants must not be disproportionate to the benefits of the research project.
c. A research project involving persons lacking the capacity to consent may be conducted only if findings of equal value cannot be obtained from research involving persons who have the capacity to consent. If the research project is not expected to bring any immediate benefit to the persons lacking the capacity to consent, the risks and stress must be minimal.
d. An independent assessment of the research project must have determined that the safety of the participants is guaranteed.

Research with human beings is often a prerequisite for the development of marketable products in life science.[64] Art. 118*b* FedCst sets out especially strict rules for (clinical) research involving human beings,[65] which includes research with human iPSCs, as well as research that includes genome editing on human iPSCs, embryonic cells or the germ line. The constitutional article highlights the requirement of a well-informed consent of the participants, their safety and the proportionality of the research. These fundamental norms are further specified in the Federal Act on Research involving Human Beings (Human Research Act, HRA) of 30 September 2011, which aims to create favorable conditions for research involving human beings and ensure its quality and transparency. Among others, the act establishes general principles, rules as to the requirements for human research, and norms on liability and data protection. The legislation is supplemented by three additional ordinances of 1 January 2014: The Clinical Trial Ordinance (ClinO), the Human Research Ordinance (HRO) and the Ordinance on Organisational Aspects of the HRA (OrgO-HRA). The ClinO covers, inter alia, clinical trials with medicinal products, transplant products, gene therapy and medical products with genetically modified organisms (GMO). The HRO covers other (i.e. non-clinical) human research projects which do not actively induce an effect on research participants. Projects might deal with biological material, deceased persons, embryos and fetuses in vitro.[66]

As stated above, the former Art. 24^{novies}, covering reproductive medicine and genetic engineering, was split into two articles: Art. 119 and 120 FedCst. For the present contribution on human iPS Cells and gene/cell therapies, Art. 119 FedCst is obviously of prime importance.

[64] Schroeder de Castro Lopes and Schallnau (2019), p. 33.

[65] For further elaborations see Schweizer, Sprecher and Straden (2022); Rütsche and D'Amico (2015); Belser and Molinari (2015b); Schweizer and van Spyk (2014).

[66] Schroeder de Castro Lopes and Schallnau (2019), p. 47.

Art. 119 FedCst Reproductive Medicine and Gene Technology Involving Human Beings

1. Human beings shall be protected against the misuse of reproductive medicine and gene technology.
2. The Confederation shall legislate on the use of human reproductive and genetic material. In doing so, it shall ensure the protection of human dignity, privacy and the family and shall adhere in particular to the following principles:
   a. All forms of cloning and interference with the genetic material of human reproductive cells and embryos are unlawful.
   b. Non-human reproductive and genetic material may neither be introduced into nor combined with human reproductive material.
   c. The procedures for medically-assisted reproduction may be used only if infertility or the risk of transmitting a serious illness cannot otherwise be overcome, but not in order to conceive a child with specific characteristics or to further research; the fertilisation of human egg cells outside a woman's body is permitted only under the conditions laid down by the law; no more human egg cells may be developed into embryos outside a woman's body than are required for medically-assisted reproduction.
   d. The donation of embryos and all forms of surrogate motherhood are unlawful.
   e. The trade in human reproductive material and in products obtained from embryos is prohibited.
   f. The genetic material of a person may be analysed, registered or made public only with the consent of the person concerned or if the law so provides.
   g. Every person shall have access to data relating to their ancestry.

Although the legislator originally focused more on reproductive medicine in Art. 119,[67] the article covers gene technology too. The term "gene technology" covers all the scientific methods which make it possible to analyse, isolate, modify, synthesise or multiply DNA, the molecular substrate of genetic information.[68] Based on this broad understanding in the Constitution, and taking into account the current methods of interpretation, human iPSCs are to be subsumed as genetic material within the meaning of Art. 119 FedCst.[69] The two fields, reproductive medicine and genetic engineering, are not necessarily linked but they do have certain interfaces, particularly in preimplantation diagnostics, prenatal diagnostics and germ line therapy. The overarching goal highlighted in para. 1 is the protection of human beings against the misuse of reproductive and gene technology. Importantly, para. 1 does not set out a prohibitory norm but is of programmatic character, placing an equal obligation on the Confederation and the cantons to fulfil the protection mandate

[67] Errass (2021), p. 5 para. 7; Reusser and Schweizer (2014b), par. 6.
[68] Reusser and Schweizer (2014b), par. 8.
[69] Sprecher (2020), p. 298.

within the scope of their responsibilities.[70] Due to rapid scientific and technological development, this is a continuous task. Art. 28 of the Federal Act on Medically Assisted Reproduction (Reproductive Medicine Act, RMA) of 18 December 1998 assigns the task to the National Advisory Commission on Biomedical Ethics (NCE). Art. 35 of the Federal Act on Human Genetic Testing of 8 October 2004 ("HGTA 2004") envisages a Federal Commission for Genetic Testing on Human Beings which, among other things, is intended to identify gaps in the legislation, provide policy advice, and follow developments in genome analysis.[71] In 2018, the Federal Assemby adopted the revised version of the Federal Act on Human Genetic Testing ("new HGTA"), which is expected to come into force in 2022. Generally, the HGTA implements the provisions of Art. 119 para. 1 and 2 FedCst and Art. 10–14 Biomedicine Convention (see Section 5.2.1.2).[72] The Act aims to protect human dignity and personality, prevent improper genetic testing and the improper use of genetic data and ensure the quality of genetic tests (Art. 1 para. 2 HGTA[73]).

Art. 119 para. 2 FedCst assigns the competence to regulate human reproductive and genetic material to the federal legislator. The term "germinal material" is to be understood broadly and includes not only germ cells (gametes, i.e. eggs and sperm cells), germ line cells, gonads (testicles/ovaries) and impregnated eggs (eggs before nuclear fusion, i.e. in a pronuclear stage) but also embryos (as from nuclear fusion until completion of organ development) and foetuses (as from organ development until birth), though not the placenta.[74] Importantly, adult stem cells only fall under federal competence if they can be reprogrammed into cells that can give rise to human life (embryos or "embryoid bodies").[75] In addition to the reproductive material, the genetic material is also protected. This includes the entirety of the genetic information of an individual contained in the DNA.

Art. 119 para. 2 lit. a–g lay down the fundamental principles in the sense of binding substantive requirements[76] regarding reproductive medicine and establish

[70] Belser and Molinari (2015c); cf. BGE 119 Ia 460, E. 5b; Federal Council's Dispatch Reproductive Medicine and Gene Technology.

[71] Reusser and Schweizer (2014b), par. 11.

[72] Errass (2021, 2022), Chapter 3, § 4, including further remarks on the HGTA; Manz C (2021), p. 27 et seq. Switzerland has not ratified the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes of 27 November 2008 (CETS No. 203).

[73] When mentioning "Art. [. . .] HGTA", this contribution refers to the HGTA which was passed by the parliament in 2018 as revision of the law of 2004 ("HGTA 2004"). The HGTA is planned to come into force in 2021. It will newly and explicitly cover genetic examinations inside and outside the medical field. In addition, the scope of the HGTA 2004 has been extended by providing a more open definition of the term "genetic examination". In the future, genetic testing will include all types of tests on the human genome (Art. 3 lit. a HGTA). In addition, data protection principles such as the right not to know genetic data will be applicable in areas of reproductive medicine, too.

[74] Art. 2 lit. e-j RMA; Reusser and Schweizer (2014b), par. 13; Biaggini (2017a), par. 7; Belser and Molinari (2015c), par. 15.

[75] Belser and Molinari (2015c), par. 15.

[76] For further information see: Schweizer (1996), par. 14 et seqq., 39 et seqq., 42.

fundamental prohibitions as to the handling of embryos. The Federal Act on Research Involving Embryonic Stem Cells (Stem Cell Research Act, StRA) of 19 December 2003 is a specification that regulates the handling of embryonic stem cells, including their generation out of surplus embryos (elaborated on further in Sect. 5.4) for research purposes. Moreover, the Federal Constitution strictly bans interventions in the genetic material of human reproductive cells and embryos (to be considered more closely in Sect. 5.4). These prohibitions imply, however, that gene therapy on born individuals, in whom the genetic material of somatic cells is altered for therapeutical purposes but not passed on to future generations, is permissible within the general limits of medical devices and treatment methods.[77] Letter b of the article prohibits the introduction or combination of non-human reproductive and genetic material into or with human reproductive material.[78] It is permitted, for instance, to introduce non-human material into somatic human cells, as well as human somatic cells into non-human hereditary or germinal material, as in the case of protein production (e.g. insulin or interferon).[79] This permission, however, is subject to the safeguard against abuse and fulfilment of the required obligations. Despite not seeming directly related to human somatic stem cells, Art. 119 para. 2 lit. c FedCst is important to take into account in the present context: when, in 2015, the constitutional revision lifted the prohibition on Preimplantation Genetic Diagnosis (PGD, in German PID), it simultaneously made gene diagnosis, the basis for the creation of human iPSCs and germ line interventions, legally possible. At the same time, the revision led to several contradictions. On the one hand, the parliament supported Prenatal Genetic Screening (PGS) which entails general screening for spontaneous non-hereditary chromosomal defects, while the constitution explicitly prohibits the selection of characteristics.[80] On the other hand, Art. 24^{novies} para. 2 lit. c FedCst, as well as the current constitution, include the imperative to prevent, to the extent possible, the creation of surplus embryos.[81] However, concurrently the revision permitted up to 12 embryos to be created during PGD with the intention of implanting one, or at most two, of the embryos deemed fittest through close observation.[82] As embryo donation is prohibited up to now,[83] this automatically leads to problematic selection processes among embryos, and healthy embryos will presumably be destroyed. Letters f and g of para. 2 provide the constitutional basis for data protection in the medical field (further elaborated on in Sect. 5.5). Importantly, genetic data generally qualifies as particularly sensitive data,[84] thus, its

[77] Belser and Molinari (2015c), par. 29.

[78] See e.g. Subbaraman (2021).

[79] Reusser and Schweizer (2014b), par. 31.

[80] For further elaborations see Staub (2019).

[81] Federal Council's Dispatch Art. 119 and PGD, p. 5942.

[82] Compare Art. 119 para. 2 lit. f. FedCst, Art. 17 para. 1 RMA: in maximum 12 embryos.

[83] Compare ECtHR, Parrillo v. Italy, 46470/11 [2015; GC], para. 167–180.

[84] Cf. Art. 5 lit. c chif. 3 revFADP; Art. 3 lit. c para. 2 FADP.

usage requires informed consent from the person concerned. In order to protect autonomy and, for example, out of concern that genetic analysis will lead to surveillance ("see-through" human beings) and thus to gene-based discrimination,[85] the provision establishes a fundamental right to informational self-determination over genetic data, including the right to know and release the raw data.[86]

Despite the prime importance of Art. 119 FedCst for human iPS Cells, the other part of the former Art. 24^{novies}, nowadays Art. 120 on non-human gene technology, should be taken into consideration by way of comparison:

Art. 120 FedCst Non-human Gene Technology

1. Human beings and their environment shall be protected against the misuse of gene technology.
2. The Confederation shall legislate on the use of reproductive and genetic material from animals, plants and other organisms. In doing so, it shall take account of the dignity of living beings as well as the safety of human beings, animals and the environment, and shall protect the genetic diversity of animal and plant species.

Art. 120 gives the Confederation the authority to issue regulations on the handling of the germinal and genetic material of animals, plants and other organisms, thereby taking into account the dignity of living beings and the safety of humans, animals and the environment.[87] The initial intention was to consider genetically modified organisms as environmentally hazardous organisms and regulate them in the Federal Environment Protection Law; but during the parliamentary debate a specific Gene Technology Act was drafted. On 21 March 2003, the constitutional provision was implemented in the Federal Act on Non-Human Gene Technology (Gene Technology Act, GTA).[88] The application of the GTA to human tissues, organs or cells is disputed.[89] As the GTA entails several security regulations which are unfortunately not included in the Stem Cell Research Act, the present contribution advocates for an analogous application to human tissues, organs or cells on the basis of the following argument: according to Art. 3 para. 1 GTA, the law applies to the handling of genetically modified animals, plants and other organisms. Art. 5 para. 1 GTA specifies that organisms are cellular and non-cellular biological units that are capable of reproducing or transferring genetic material.[90] The broad

[85] Gallegos López (2011) passim.

[86] Cf. Art. 4-9 HGTA (applicable accordingly in relation to the RMA, HRA).

[87] For detailed elaborations on Art. 120 FedCst, see, for instance, Schweizer and Errass (2014); Waldmann (2015); Errass (2021), para. 5 et seq.

[88] A moratorium on genetically modified plants, plant parts, seeds and animals has been in force since 2005. It was last extended by federal decree on 29 August 2016 and a second time in 2021 (see Federal Council's Dispatch 19.4225). The moratorium is now valid until 31 December 2025 [Art. 37a GTG; Biaggini (2017b), par. 7; Waldmann (2015), par. 2; Schweizer and Errass (2014), par. 2].

[89] Cf. against the application Errass (2006), p. 137.

[90] Federal Council's Dispatch Environment Protection Law, BBl 1993 II, p. 1468.

term[91] includes single- and multi-cellular organisms and non-cellular biological entities such as viruses and cell cultures. Human iPSCs are capable of transferring genetic material (at least with an external influence—one could thus speak of "dependent organisms") and may exist as cell cultures. They thus could qualify as organisms, more specifically as genetically modified organisms in terms of Art. 5 para. 2 GTA. If humans iPScs are used outside the human body or are developed further extracorporeally the present contribution argues in favour of applying the GTA by analogy, because it promotes a step-by-step approach, demands full transparency and also offers specific liability rules. Art. 6 GTA and Art. 10–12 GTA set out general principles regarding the release for experimental purpose as well as for market placement in order to protect human beings, animals, the environment and biological diversity. In addition, in such cases, the Human Research Act sets out a number of important provisions regarding the further use of human cells or tissue, based on protection of personality and data protection (cf. Art. 32–35 HRA).

Further important in the regulatory framework of human iPSCs-usage is Art. 119a FedCst on transplant medicine.

Art. 119*a* FedCst Transplant Medicine

1. The Confederation shall legislate in the field of organ, tissue and cell transplants. In doing so, it shall ensure the protection of human dignity, privacy and health.
2. It shall in particular lay down criteria for the fair allocation of organs.
3. Any donation of human organs, tissue and cells must be free of charge. The trade in human organs is prohibited.

Art. 119*a* para. 1 gives the Confederation the comprehensive competence (with retroactive derogatory effect) to regulate the entire transplantation system which, being part of the public health system, is traditionally the responsibility of the cantons. The scope of application *ratione materiae* includes the transplantation of organs, tissues and cells, i.e. all possible transplants intended for transplantation to humans.[92] Based on Art. 119*a*, the Federal Act on the Transplantation of Organs, Tissues and Cells (Transplantation Act), which sets out the requirements for the use of organ tissues or cells for transplantations purposes (Art. 1 para. 1), was introduced on 8 October 2004. Importantly, the act is not applicable to germ cells, impregnated ova and embryos for medically assisted human reproduction.[93] The Transplantation

[91] Federal Council's Dispatch Environment Protection Law, BBl 1993 II, p. 1468.

[92] Schott and Schweizer (2014), par. 8 et seq.

[93] The Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin (ratified by Switzerland on 10 November 2009; SR 0.810.22) also excludes reproductive organs and tissues, as well as embryonic or fetal organs and tissues, from its application in Art. 2 para. 2 lit. a and b.

Act was supplemented by the Transplantation Ordinance[94] of 16 March 2007. These regulatory provisions replaced prior, fragmented norms and regulated the transplant services in a uniform and comprehensive manner.[95] Both regulations define the term "transplant product", which covers tissues and cells that have either been substantially engineered to achieve biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement, or which are not intended to perform the same function in the receiving person as in the donor (this includes autologous settings as well;[96] Art. 2 para. 1 lit. d Transplantation Ordinance). This definition is in accordance with European Regulation (EC) No. 1394/2007.[97] IPS Cells are characterised by reprogramming, possible genetic engineering and a subsequent differentiation into other cell types. Therefore, they have been substantially engineered and may perform a different function than in their original form.[98] According to current information from Swissmedic, the Swiss Agency of Therapeutic Products, the regulation of transplant products by the TPA and the corresponding ordinances make no distinction with regard to the regulation of human iPSCs as gene/cell therapy products. Novel technologies, such as the European advanced therapy medicinal products (ATMP), are understood as transplant products in Switzerland.[99]

To summarise, numerous acts must be considered when handling iPS Cells. Following the classification of iPS Cells and cell/gene therapies using iPS Cells as transplant products, the norms of the Transplant Act and the Therapeutic Products Act and their implementing ordinances apply. As examined above, there are standards based on cumulatively applicable articles and implementation regulations, e.g. on human research and the conduct of clinical studies, as well as on data protection. Under the conditions set out in these norms, somatic gene therapy on born people, in whom the genetic material is altered for therapeutic purposes and without intervening in the genetic material of future generations (prohibition of germ line intervention in Art. 119 para. 2 lit. a FedCst), is allowed.[100] In terms of the permitted lower limit with regard to the prohibition on chimera formation (Art. 119 para. 2 lit. b FedCst), it is also permissible to convert genome-edited somatic cells into non-human hereditary or germinal material, as in the case of protein production (e.g. insulin or interferon).[101]

[94] Note that the ordinance is only available in German. The original title is "Verordnung über die Transplantation von menschlichen Organen, Geweben und Zellen (Transplantationsverordnung)".

[95] Schott and Schweizer (2014), par. 13.

[96] Marti (2015), p. 134.

[97] Cf. Federal Office of Public Health (2016), p. 1; Swissmedic (2019d); Mumme et al. (2020), p. 90.

[98] Also see Chumrec (2018), p. 59.

[99] Mumme et al. (2020), p. 89.

[100] Belser and Molinari (2015c), par. 29.

[101] With further information Reusser and Schweizer (2014b), par. 31.

The scientific environment is characterised by cross-border research projects and international exchange.[102] Therefore, besides relevant national norms, international regulations are highly significant and authoritative. In the present context, the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: the Convention on Human Rights and Biomedicine (The Biomedicine Convention, Oviedo Convention) of 1997, the only international legally binding norm dealing with human rights in biomedicine, must be mentioned.

5.2.1.2 The Biomedicine Convention

The Biomedicine Convention aims to guarantee human rights and human dignity in the field of biology and medicine and thus supplements the European Convention on Human Rights.[103] It contains core principles; more specific provisions are to be included in the additional protocols (Art. 31).[104] Switzerland ratified the Biomedicine Convention on 24 July 2008, and it came into force on 1· November of the same year.

The central element of the Convention is the "protection of the genetic identity of nascent human life and the recognition of human autonomy" (Art. 1). Art. 2 states that the interests and welfare of the human being[105] take precedence over the interests of society or science alone. For Switzerland, the convention is partly self-executing, meaning that it applies in part without transposition into national law and individuals can refer directly to it.[106] In principle, it is up to the authorities applying the law to take binding decisions on the justiciability of the provisions of the Convention in individual cases. However, the Federal Council assumes that the core norms of the Biomedicine Convention, i.e. Art. 5–9 on consent, Art. 10 para. 1 and 2 on the protection of privacy and the right to information, Art. 11–14 on the human genome, Art. 15 on freedom of research, Art. 16 and 17 on the protection of persons in research projects, Art. 18 para. 2, which prohibits the creation of embryos for research purposes, Art. 19 and 20 on organ and tissue transplantation, Art. 21 on the prohibition of financial gain and Art. 22 on the use of a human body part are, in principle, directly applicable.[107]

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[102] Constantin and Andorno (2020).

[103] Preamble Biomedicine Convention; Federal Council's Dispatch Biomedicine Convention and Cloning, 280, 283; Errass (2021), Chapter 2, § 2, including further elaborations on the Biomedicine Convention; Radau (2006), pp. 19 et seqq., 33 et seqq.

[104] Federal Council's Dispatch Biomedicine Convention and Cloning, 283.

[105] It is important to note that Art. 2 explicitly mentions "human beings" and not, for example, "human life". Thus, unborn human life seems to be covered by the Ovideo Convention; cf. Radau (2006), p. 213. Comparable, outside the medical context of abortion, is the view of the ECtHR, Vo v. France, 53924/00 [2004], para. 87.

[106] Tschannen (2016), par. 4 et seq.

[107] Federal Council's Dispatch Biomedicine Convention and Cloning, p. 285.

In addition to the Biomedicine Convention, Switzerland has ratified the Additional Protocol on the Transplantation of Organs and Tissues of Human Origin, as well as the Additional Protocol on the Prohibition of Cloning Human Beings. Art. 1 of the latter prohibits any intervention "aimed at producing a human being genetically identical to another human being, living or dead" (both living beings possess the same nuclear genome). The international relevance of the prohibition can be seen by its inclusion in the Charter of Fundamental Rights of the European Union (Art. 3 para. 2), as well as in the United Nations Declaration on Human Cloning.

Switzerland has, however, not yet ratified the two remaining Additional Protocols of the Biomedicine Convention, namely the protocols concerning Biomedical Research and on Genetic Testing for Health Purposes.

5.2.2 Regulatory Authorities

After examining the regulatory framework on human iPS Cells and gene/cell therapies using human iPSCs in Switzerland and prior to analysing the specific regulatory prerequisites, it seems valuable to present the authorities which implement and execute the standards.

5.2.2.1 Federal Office of Public Health

The Federal Office of Public Health (FOPH), attached to the Federal Department (Ministry) of Home Affairs, is responsible for the development, execution and control of the laws and ordinances that are based on the norms set out in the federal constitution. The FOPH is thus responsible for social health and accident insurance, regulations on chemicals, medicines, legislation in the areas of biosafety, research on humans and transplantation medicine, health promotion, national programmes combating addiction and sexually transmitted diseases, radiation protection, and the regulation of university medical and health professionals. Apart from that, the FOPH represents the country's interest in health matters in the international context.[108] Within these broad work areas, the FOPH is responsible for the authorisation of transplantation of human organs and the authorisation for the storage, import and export of human tissue, cells or organs including embryonic or foetal ones.[109]

[108] Federal Office of Public Health (2018f).

[109] Art. 25, Art. 27, Art. 36, Art. 38, 43, 65 Transplantation Act; Federal Office of Public Health (n.d.).

5.2.2.2 Swissmedic

As Switzerland is not a member of the European Union but is only associated through an important number of bilateral treaties, it has its own approval authority for medicinal products and medicinal devises: Swissmedic, the Swiss Agency for Therapeutic Products.[110] However, Swissmedic often acts according to the practice of the US National Institutes of Health (NIH) and the European Medicines Agency (EMA). Thus, Swissmedic is the enforcement entity regarding the legislation on therapeutic products. The institute is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Its competences encompass authorisation of medicinal products, licensing of manufacturing and wholesale, inspections and market monitoring, establishing standards for clinical trials as to the quality of medicines and information. Before granting authorization for gene therapy products, the Agency shall seek opinions from the Swiss Expert Committee for Biosafety (SECB), the Federal Office for the Environment (FOEN) and the FOPH (Art. 35 para. 2 ClinO).[111]

5.2.2.3 Swiss Ethics Commissions

In Switzerland, seven Cantonal Ethic Commissions (CECs) investigate whether a planned research project involving research on human beings in their respective regions[112] is in line with the applicable regulations. If the requirements are met, the Ethics Commissions issue authorisations.[113] The specific requirements and procedures will be explained below. In terms of organisation, the seven ethics commissions are mainly organised by the cantonal health directorates or social departments. They are supervised by the respective cantonal and state councils, or by the health departments themselves. Some commissions such as Berne, Geneva and Ticino are administratively attached to the Cantonal Pharmacy Office. In Northwest and Central Switzerland, supervision is the responsibility of an intercantonal body set up by the health directorates of the affiliated cantons.[114]

[110] As the FOPH, the agency is attached to the Federal Department of Home Affairs.

[111] Cf. Art. 5, Art. 9 set seqq.; Art. 18 et seqq.; Art. 28; Art. 34 et seq., Art. 54; Art. 64 TPA; Art. 49 Transplantation Ordinance in conjunction with the TPA; Swissmedic (2019c).

[112] Berne, Northwest and central Switzerland (EKNZ), East Switzerland (EKOS), Geneva (CCER), Ticino as well as Valais and Fribourg; Art. 47 HRA; see a list of the cantonal ethic commissions on the website of Swissethics, a joint association: https://swissethics.ch/en/ethikkommissionen.

[113] Cf. Art. 45 et seqq., Art. 51 et seqq. HRA.

[114] Koordinationsstelle Forschung am Menschen (2018), p. 8; the report offers further insights into the work of the ethics commissions in 2018, including statistics e.g. about the number of approved research projects.

5.3 Regulatory Prerequisites for Combined Gene/Cell Therapy Using Genome Edited Human iPS Cells to be Differentiated into Somatic Cells

The following section will examine the regulatory prerequisites and administrative procedures for combined gene/cell therapies in Switzerland. In order to provide an accessible overview, the subsequent section is structured "follow[ing] the value chain, 'from the bench to the market'".[115] Hence, the general principle of informed consent (Sect. 5.3.1), the requirements for clinical trials (Sect. 5.3.2), market placement (Sect. 5.3.3) and patentability (Sect. 5.3.4) will be analysed in detail below.

It should be born in mind that all these steps involve prior genetic testing. According to the HGTA, anybody carrying out molecular genetic investigations in the medical field requires a licence from the Federal Office of Public Health (FOPH), which demands that necessary technical and operational requirements are met and that an appropriate quality management system is in place (cf. Art. 28 HGTA). As a result of the general principle of informed consent (Sect. 5.3.1 in detail) these genetic investigations need to be accompanied by non-directive, expert genetic counselling before and after implementation. The consultation must be documented (Art. 21 para. 2 HGTA).[116] As stated above, genome editing e.g. via CRISPR/Cas9, is permitted in somatic cells in Switzerland pursuant to Art. 119 FedCst. However, there is no explicit norm setting out the regulatory requirements for the editing process. According to current information from Swissmedic, retransplantation to the patient does not require further notification.

5.3.1 The General Principle of Informed Consent

Prior to the specific prerequisites, the general principle of *informed consent* is worth a detailed elaboration as it is relevant for all processes related to the handling of human genetic material, for example, the genetic testing prior to a gene/cell therapy using genome edited human IPSCs.[117]

[115] Schroeder de Castro Lopes and Schallnau (2019), p. 1. The authors provide a highly significant and very useful practical guide on the regulations of life science law in Switzerland, as well as meaningful considerations on the current cutting-edge questions. The present section is organised following their structure.

[116] For an insightful discussion on the degree of autonomy that the individual has with regard to genetic analyses and the HGTA, see Junod and Romagnoli (2016), pp. 227–245.

[117] Closely related to the principle of informed consent for medical measures, is the principle of necessary consent to disclose personal data. (Cf. Art. 27 revFADP, Art. 13 para. 1, Art. 4 para. 5 FADP; Art. 16 et seq., 32–34 HRA; Art. 5 HGTA; Art. 8, 57–60 Transplantation Act; Art. 321bis para. 1 Criminal Code).

The basis of all treatment and research on human beings is the right of people to self-determination over their health and life. This autonomy results in the requirement that the *informed consent* of the person concerned must be available prior to a health measure (except for emergencies). As the central point of any medical-biological measure, the principle is secured in Art. 5 Biomedicine Convention[118] as well as Art. 119 para. 2 lit. f and Art. 118b para. 2 lit. a FedCst and is concretised in federal and cantonal laws.[119]

Art. 5 General Rule

1. An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it.
2. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks.
3. The person concerned may freely withdraw consent at any time.

In order to consent to a research project, patients need to be adequately informed about the project.[120] The HRA, for instance, includes further details about the information that is required to be given prior to the consent.[121]

Art. 16 para. 2

2. The persons concerned must receive comprehensible oral and written information on:
   a. the nature, purpose and duration of, and procedure for, the research project;
   b. the foreseeable risks and burdens;
   c. the expected benefits of the research project, in particular for themselves or for other people;
   d. the measures taken to protect the personal data collected;
   e. their rights.

Even stronger requirements are included in the new HGTA which demands comprehensive information for genetic testing (Art. 6 in conjunction with 5, 23 and 32 HGTA). Included are information on the purpose and significance of the investigation; on risks as well as physical and mental stress associated with the investigation; on the handling of the sample and the genetic data during and after the examination; on surplus information; on the possible significance of the results of the investigation for family members and their right not to know; and lastly on the

[118] For biomedical research, the principle is concretised in Art. 13 et seq. Additional Protocol Biomedicine Convention on Biomedical Research.

[119] Art. 6, 7 16 et seqq., 26 and 32 para. 1 HRA; Art. 5 para. 1, 6 HGTA; Art. 5 para. 6 revFADP, Art. 4 para. 5 FADP; van Spyk (2011), pp. 106 et seq. Note that the HRA is not applicable to anonymised genetic and biological data (Art. 2 para. 2 HRA).

[120] Manaï (2013), pp. 79 et seqq.; Rosenthal and Jöhri (2008), par. 6; Radau (2006), p. 56 et seqq. on Art. 5 Biomedicine Convention.

[121] Sprecher and van Spyk (2015), pp. 270–289.

patient's rights, in particular with regard to consent, information and not knowing. In case of an insufficient information, e.g., a genetic testing has been conducted unlawfully.[122]

The requirement of an informed consent begins with the procurement of human cells and tissues for stem cell and embryo research; the information should indicate the source of the material and the aims of its use for research purposes[123] (compare Art. 5 StRA as well Art. 7 HRA concerning the consent, Art. 36 HRA concerning research on deceased persons and Art. 39/40 HRA concerning research involving embryos and foetuses). The general conditions of an informed consent are regulated in Art. 5 StRA as well as in Art. 7 HRA, and there are specific requirements in Art. 5a–6a RMA on duties to inform and counsel on the techniques of medical assisted reproduction, in Art. 36 HRA concerning research on deceased person, in Art. 39/40 HRA concerning research involving embryos and foetuses and in Art. 2a TPA (revised an 22 March 2019) concerning the use of devitalised cells and tissues. If persons are not able to consent to research, Art. 6 and 17 Biomedicine Convention and Art. 24 HRA must be respected.[124]

Following this comprehensive information, free and explicit consent is required. The consent is recognized as free if neither unauthorized pressure nor deception led to it.[125] It is explicit, when it is given to a particular person and relates to specific data.[126] Following the principle of self-determination, the consent may further be revoked at any time (cf. Art. 5 para. 2 HGTA). One may state, therefore, that the main principle followed by the legislator is the final control by the patient over his health data and the understanding that the patient is actually capable of exercising this right.[127] This implies that the requirement of consent demands the capability of judgment of the affected person.[128] At the same time, this means that special requirements need to exist for people who are uncapable of judgment.[129] The Biomedicine Convention, for instance, includes such prerequisites in Art. 6 and 7.[130]

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[122] Errass (2021, 2022), Chapter 3, § 7 III.

[123] ISSCR Guidelines (2021), para 2.3 Procurement and Informed Consent of Human Biological Materials, Appendix A3. Informed Consent Considerations for Procurement of Cells and Tissues for Stem Cell Research and Translation.

[124] Schweizer RJ (2020b), pp. 210 et seqq.

[125] Errass (2021, 2022), Chapter 3, § 7 III; van Spyk (2011), pp. 233 et seqq.; Federal Council's Dispatch HGTA 2017, p. 5658.

[126] Manaï (2013), pp. 65 et seqq.

[127] Aebi-Müller (2020), p. 6.

[128] From the age of 12 years on, the capability of judgment is—refutably—presumed in the case of simple medical interventions, otherwise at the most from the age of 16 years on (Aebi-Müller 2014, par. 44–46; Gächter and Rütsche 2018, par. 25).

[129] Cf. e.g. ECtHR, Fernandes de Oliveira v. Portugal, 78103/14 [2019], para. 104–115.

[130] See Aebi-Müller (2014) for further detail on the patient, uncapable of judgment; Radau (2006), pp. 55 et seqq. See then van Spyk (2011), pp. 253 et seqq. on the exceptional admissibility of research without "informed consent" and pp. 291 et seqq. on the possible infeasibility of research despite "informed consent".

5.3.2 *Clinical Trials*

After preclinical testing, clinical tests on human beings are required for the authorisation of transplant products,[131] as which human iPSCs qualify.[132] Clinical trials, or clinical studies, are defined as research projects in which persons are prospectively assigned to a health-related intervention in order to investigate its effect on health, or on the structure and function of the human body (Art. 3 lit. 1 HRA). Besides the HRA and the ClinO, other regulations are of great importance (Table 5.1).

For human iPSCs and gene/cell therapies using human iPSCs, the following is important to keep in mind: the prerequisites set out in the ClinO for trials with medicinal products apply *mutatis mutandis* to the testing of transplant products, as which human iPSCs qualify (Art. 21 ClinO). Furthermore, according to Art. 49 para. 1 Transplantation Act, the TPA, and as such the Ordinance on Therapeutic Products and the Ordinance on Licensing in the Medicinal Product Sector (Medicinal Products Licensing Ordinance, MPLO), apply to transplant products.

5.3.2.1 General Principles of Clinical Trials

In order to protect the dignity, health and privacy of the participants in human research projects, certain general principles need to be complied with in all projects:[133]

- **Principle of self-determination and informed consent:** As stated above (Sect. 5.3.1) the principle of informed consent is crucial and decisive in any treatment with patients, and it is a basic requirement for clinical trials. Thus, on the one hand, a comprehensive explanation of, *inter alia*, the objectives and risks of the study,[134] and, on the other hand, the free, written and prior consent thereto, is demanded.[135]
- **Principle of subsidiarity, proportionality and risk-benefit analysis:** According to the principle of subsidiarity, the rights, well-being and safety of the trial subjects take precedence over the interests of science and society, and thus research may be carried out only if equivalent findings cannot be obtained by other means. While there is a need for research involving human subjects, this must never lead to subjects being completely or temporarily deprived of

[131] Mumme et al. (2020), p. 93.

[132] For a comprehensive and cross-disciplinary contribution on the clinical application of human IPSCs, see Gerke et al. (2020).

[133] Schroeder de Castro Lopes and Schallnau (2019), p. 48.

[134] Art. 5 Biomedicine Convention; Art. 13 et seq. Additional Protocol Biomedicine Convention on Biomedical Research; Art. 7 HRA; modifications based on Art. 18, 30 HRA.

[135] Art. 16 HRA.

Table 5.1 Overview of the relevant regulations for clinical trials including iPS cells [partly following Schroeder de Castro Lopes and Schallnau (2019), pp. 34 et seq.]

Main Swiss regulations	Art. 118*b* FedCst	Sets out the general principles of human research
	HRA	The main federal law on human research
	ClinO	Regulates the requirements for the conduct of clinical trials as defined in the HRA, the authorisation procedure and the registry of trials
	OrgO-HRA	Focuses mainly on the responsibility of the ethics commission for research
Other relevant Swiss regulations	TPA and ordinances	Sets out complementary criteria for clinical trials needed to market a product, e.g. manufacturing licence MPLO
	OrgO-HRA	Does not apply to genetic testing performed for research purposes, but aims to ensure the quality of tests
	Transplantation Act and ordinances	Complementary provisions
	(StRA)	(specific conditions for the use of human embryonic stem cells for research purposes)
	(RMA)	(prohibition on the misuse of bio-technology and gene technology, strict conditions for analysing reproductive cells)
International regulations	Council of Europe: Biomedicine Convention	Includes principles and rules for clinical research
	European Medicines Agency: ICH guideline E6 on good clinical practice[a]	Sets a quality standard for clinical trials with human subjects
	European Commission: GMP Directive[b]	Establishes the requirement of a manufacturing authorisation for all investigational medicinal products for human use

[a]Draft of 24 June 2021: EMA/CHMP/ICH/337843/2021; former version: Guideline for good clinical practice E6(R2) of 1 December 2016: EMA/CHMP/ICH/135/1995
[b]Commission Directive 2003/94/EC of 8 October 2003

medically necessary preventive, diagnostic or therapeutic treatments.[136] Further to the principle of proportionality, the risks and burdens for the participants of a trial must be minimised as far as possible and may not be disproportionate to the expected benefits of the research.[137] In short, the research project needs to be evaluated according to a risk-benefit analysis. This principle can be found in all

[136]Cf. Art. 11 HRA, Art. 16 lit i, 17 para. 1 lit. i Biomedicine Convention; Art. 5, 23 Additional Protocol Biomedicine Convention on Biomedical Research.

[137]Art. 12, 15 HRA; already enshrined in Art. 5 para. 2, Art. 36 para. 3 FedCst.

international regulations, i.e. in the Helsinki Declaration (Art. 16–18) or the CIOMS[138]-Guideline 7.

- **Principle of scientific relevance and scientific standards:** According to an internationally recognised principle,[139] research on human beings must address a scientifically relevant issue. According to Art. 5 HRA, a relevant question has to relate to the understanding of human diseases, the function of the human body or public health. According to Art. 10 HRA, in order to evaluate a project's scientific value, the research question, scientific integrity, independence and adequate training and qualifications of the investigators need to be considered. Importantly, scientific relevance does not depend on the profitability of the research. On the contrary, in line with the idea of fair research promotion, unprofitable research areas should not be neglected (Additional Protocol Biomedicine Convention on Biomedical Research[140]). Related to the principle of scientific relevance is the obligation to document the research projects correctly,[141] as well as the imperative of verifiability and the publication of results and studies.[142] The WHO Expert Committee underlines the need of "a cultural change around reporting of possible illegal unregistered, unethical or unsafe research and other activities. This requires reinforcing efforts to promote research integrity and best practices".[143]
- **Principle of non-discrimination:** This principle, already mentioned under the provisions on fundamental rights, is confirmed by Art. 1 para. 1 Biomedicine Convention. In connection with test persons unable to give consent, a refusal to participate, a refusal or withdrawal of consent on the part of the legal representative may not lead to discrimination (particularly in medical care) against the persons concerned.[144]
- **Principle of non-remuneration and compensation:** In order to protect participants from impermissible ties and dependencies, the effort of the test persons has to be compensated, but an "inducement to participate in research" is not allowed.[145] The principle is supplemented with the prohibition on trade in human reproductive material and products obtained from embryos.[146] In addition

[138] Council for International Organizations of Medical Sciences.

[139] Art. 8 in conjunction with Art. 1 Additional Protocol Biomedicine Convention on Biomedical Research; CIOMS-Guidelines 19 und 20; GCP-Guideline No. 2.5.

[140] Cf. CIOMS-Guideline 10.

[141] Cf. GCP-Guidelines No. 2.5, 2.10; Art. 11 Additional Protocol Biomedicine Convention on Biomedical Research.

[142] Cf. Art. 28 Biomedicine Convention Protocol on Biomedical Research; Art. 27 Helsinki-Declaration.

[143] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing (2021), point 2.5, p. 12 et seq.

[144] Art. 15 para. 3 Additional Protocol Biomedicine Convention on Biomedical Research.

[145] Cf. CIOMS-Guideline 7.

[146] Art. 119 para. 2 lit. e FedCst.

to adequate compensation, participants need to be compensated for damages, including the management of long-term consequences.[147]

- **Principle of punishment of criminal acts:** Following binding international acts, judicial protection against abusive research and appropriate legal sanctions in the event of violations must be provided for (e.g. Art. 24 et seqq. StRA;[148] Art. 62 and 63 HRA and Art. 29 et seqq. RMA[149]).
- **Principle of prohibition of medical and scientific experimentation:** In accordance with Art. 7 sent. 2 CCPR, any form of physical or mental mutilation and any form of medical or scientific experimentation on a defenceless or otherwise vulnerable person against her or his will is prohibited.[150]
- **Additional requirements for studies involving vulnerable persons:** For research projects involving vulnerable people, i.e. children, adolescents and adults lacking capacity,[151] pregnant women,[152] prisoners[153] and emergency patients,[154] particular requirements, which are specified in Art. 21 HRA, must be respected during the consent procedure. Moreover, such research may only be carried out if equivalent findings cannot be obtained with non-vulnerable participants (Art. 11 para. 2 HRA).[155]
- **Principle of prior research approval:** All international rules and national norms set out the principle of prior approval and authorisation for research with human beings.[156] In order to provide more detailed and practical insights, this aspect is further explained below.

5.3.2.2 In Particular: Preclinical Studies

ISSCR, the International Society for Stem Cell Research, recommends strongly in their Guidelines for Stem Cell Research and Clinical Translation of May 2021 the performance of non-human animal studies prior to any clinical trial. “Before initiating clinical studies with stem cell-based interventions in humans, researchers should have persuasive evidence of safety and the potential for clinical utility in appropriate in vitro and/or animal models. These preclinical studies must be rigorously designed

[147] Art. 24 Biomedicine Convention; Art. 31 Additional Protocol Biomedicine Convention on Biomedical Research.

[148] Federal Act on Research Involving Embryonic Stem Cells (Stem Cell Research Act, StRA).

[149] Federal Act on Medically Assisted Reproduction (Reproductive Medicine Act, RMA).

[150] See Schabas WA (2019), Art. 7.

[151] Art. 21 et seqq. HRA in conjunction with Art. 3 lit. j and k HRA.

[152] Art. 25 et seqq. HRA.

[153] Art. 28 et seq. HRA.

[154] Art. 30 et seq. HRA.

[155] On the non-judgemental patient, see Aebi-Müller (2014); Manaï (2013), pp. 195 et seqq.

[156] Cf. HRA; CIOMS Guideline 2; Art. 9 Additional Protocol Biomedicine Convention on Biomedical Research.

and have been subject to regulatory oversight and reviewed independently prior to the initiation of clinical trials. This helps ensure that trials are scientifically, medically, and ethically warranted.[157]

5.3.2.3 Prior Research Approval

Prior to commencing clinical trials, the project must be reviewed in Switzerland by an independent ethics committee, the Cantonal Ethics Commissions (cf. Sect. 5.2.2) of the Canton where the research is conducted (Art. 47 para. 1 HRA). The CECs primarily examine whether scientific, legal and ethical requirements are met (Art. 45 para. 2 HRA, Art. 25 ClinO). There is a distinction between two types of authorisations: on the one hand, an authorisation to carry out a research project, either prospectively or retrospectively (e.g. projects in which the biological material has already been removed) and, on the other hand, an authorisation to re-use the material for research purposes in the absence of consent or information on the right of objection.[158] The Ethics Commission shall acknowledge receipt of the application within 7 days and notify the investigator of any formal deficiencies in the application documents. Within 30 days of acknowledging receipt of the formally correct application for research on a cell therapy without risks on heritable changes of the human genome, the commission decides on the authorisation (Art. 26 ClinO). The evaluation of research involving genome editing of human somatic stem cells, and especially the evaluation of research that involves gene alteration of a human embryo or human gametes, or the review of research that involves in utero stem cell and gene editing intervention or of other research on gene therapies, need special procedures, which have not yet been determined in Swiss Law, and these evaluations need in any case more time; they must be also in accordance with the Guidelines 2021 of the International Society of Stem Cell Research (ISSCR).

Besides the prior approval by the relevant CEC, clinical trials require an authorisation from Swissmedic depending on their categorisation (Art. 54 para. 1 TPA, Art. 3 TPAO, Art. 30 et seq. ClinO): according to the HRA, clinical trials, including those using transplant products, are classified according to the type of human research project and the existent knowledge of Swissmedic into Group A, B, C (Art. 19 ClinO). The classification determines which approval procedure a project

[157] The ISSCR Guidelines explain: "Cell-based interventions offer unique challenges for preclinical studies. In some cases, homologous cells in the same species are unavailable. Immunesuppressed animal models, while useful, do not permit an understanding of the effect of the immune system on transplanted cells, or, more often, they may not share all the same biological properties of their human counterparts. Since transplanted cells are considerably more complex and can change after transplantation in unpredictable ways, extrapolating cell therapies in an animal model to humans is even more challenging than for small molecule therapeutic candidates." Guidelines 2021 § 3.3, p. 27.

[158] Jenni (2015), par. 3.

must undergo and which official requirements must be met.[159] Group A trials use medicinal products authorised in Switzerland and in accordance with the Swiss summary of product characteristics (SmPC). These projects do not require approval from Swissmedic (Art. 30 ClinO), but only from the CEC.[160] Clinical trials of category B use medicinal products authorised in Switzerland but not according to the Swiss SmPC. Besides the approval from the CEC, they require an authorisation from Swissmedic.[161] Clinical trials of Category C are research projects with medicinal products that are not authorised in Switzerland. They also require both authorisations.[162] Depending on the group, higher liability coverage is required for each person, for property damage and for the entire clinical trial.[163] During the authorisation procedure, Swissmedic examines whether the requirements of good manufacturing practice and those relating to the safety of medicinal products apply. Furthermore, it investigates whether the requirements set out in Art. 45 TPA have been met, i.e. whether the clinical trial takes into account the product risks, as well as whether the product data is state of the art and has been correctly reflected in the trial protocol (Art. 30 ClinO, 54 para. 4 TPA). As in the case of the Ethics Commission, Swissmedic acknowledges receipt of the application within 7 days and notifies the investigator of any formal deficiencies in the application documents. The commission decides on the authorisation within 30 days of having acknowledged receipt of the formally correct application (Art. 33 ClinO).

5.3.2.4 Conducting the Clinical Trial: Notification and Documentation

At any time during the trial, Swissmedic may carry out an inspection to evaluate whether the conduct of the clinical trial meets the requirements of this law and those of the HRA (Art. 46–48 ClinO; Art. 54 para. 5 TPA). The relevant CEC and authorities shall be informed prior to the inspection and may also participate (Art. 46 para. 2 ClinO). Swissmedic may revoke or suspend the authorisation granted or, if needed, subject the continuation of the clinical trial to additional conditions (Art. 47 ClinO).

Depending on the risks of the clinical trials, the sponsors and investigators must comply with certain requirements while the project is being carried out.[164] Clinical trials require a notification to the CEC and—for Category B and C—to Swissmedic

[159] The Swiss coordination authority for research on human beings (kofam) provides a useful online categoriser: https://www.kofam.ch/en/categoriser/.

[160] The mandatory documentation is described in Annex 3 No. 1 ClinO.

[161] The documentation needed for the CEC is set out in Annex 3 No. 2 ClinO, the prerequisites regarding Swissmedic are defined in Annex 4 No. 1.

[162] The necessary documentation regarding the CEC is also set out in Annex 3 No. 2 ClinO, the prerequisites regarding Swissmedic are defined in Annex 4 No. 2.

[163] For extensive explanation on the application process and the legal requirements for gene therapy and transplant products see Marti (2015), pp. 134 et seqq.; See Annex 2 ClinO.

[164] Schroeder de Castro Lopes and Schallnau (2019), pp. 58 et seq.

in case immediate safety and protective measures are taken during the clinical trial (Arts. 15 para. 2 HRA, 37 ClinO, 20 HRO), as well as when the trials are completed, discontinued or interrupted (Art. 38 ClinO, 22 HRO). Moreover, a notification to Swissmedic is required if adverse events or a suspected unexpected serious adverse reaction occurs (Art. 49 Transplantation Act in conjunction with Art. 3 and 59 TPA). In this context special considerations concern the tumorigenic potential of the transplant product; in vitro and in vivo studies must be performed to identify and evaluate this risk.[165] This notification is required independent of whether the application is allogenic or autologous. Specific requirements depend on the severity of the events and the therapeutic products affected.[166] Apart from that, significant changes to an authorised trial require an authorisation from the agency (Art. 34 ClinO). The actual transplantation of transplant products, however, is not subject to reporting.

5.3.2.5 Manufacturing

As stated above (Sect. 5.3.1) the TPA and the relevant ordinances, as such the MPLO, apply to human iPSCs as transplant products. *Inter alia* these legal sources set out the necessary requirements for the manufacturing of medicinal products (and transplant products),[167] including when they are used for clinical trials. Manufacturing, thereby, includes all stages of the manufacturing process from the acquisition of the precursor to the delivery of the end product (Art. 4 para. 1 lit. c TPA), According to Art. 5 para. 1 TPA the manufacturing requires a licence of Swissmedic, which shall be issued if the necessary technical and operational conditions are fulfilled and an appropriate quality assurance system exists (Art. 6 TPA). The specific requirements are described in more details in Art. 3 et seq. MPLO. The MPLO includes conditions regarding—inter alia—a system for quality assurance, the minimum number of qualified workers and facility organisation further to the requirements of Good Manufacturing Practice (GMP). The GMP requirements ensure that products are consistently produced and controlled according to quality standards. They are described in Annex 1 and 2 of the MPLO, which also include relevant international GMP rules. It is especially important to control the quality and purity of the material, the cells, and to check for possible cellular or noncellular impurities of each material in the final product.[168] To guarantee the standards, a person must be trained and technically supervise the facilities and ensure that the medicinal products are

[165] Marti (2015), p. 142.

[166] For reporting obligations to the CEC consult Swiss Academy for Medical Science (2015); for reporting obligations to Swissmedic see Swissmedic (2019b).

[167] Concerning the distinction between transplants (as e.g. cardiovascular tissues) and transplant products (as e.g. an ex vivo or ex vitro gene therapy product with cells that have been genetically modified) see Appendix 1 of the EU Regulation (EC) 1394/2007 of 13 November 2007; Marti (2015), pp. 135 et seqq., and pp. 140 et seqq. concerning transplant products and gene therapy products respectively.

[168] Marti (2015), p. 141.

handled appropriately. Swissmedic carries out regular inspections to make sure that the regulations are being complied with.[169]

According to Art. 7a para. 2 TPA, hospital pharmacies must hold a manufacturing licences that cover at least the manufacture of medicinal products in accordance with Art. 9 para. 2 TPA, including medical products intended for clinical trials (lit. d). They are further required to must carry out a risk assessment in accordance with Annex 3 of the MPLO. Depending on the results a cantonal manufacturing licence is required instead of a licence issued by Swissmedic (Art. 8 para. 1 and 3 MPLO).

5.3.2.6 Liability in Cases of Damage

According to Art. 19 HRA, "any person who carries out a research project involving persons shall be liable for damage suffered by them in connection with the project". The HRA thus imposes the principle of strict liability regardless of fault.[170] As described above, liability insurance in accordance with Art. 20 HRA, and depending on the risks of the project, is required. The person liable is the sponsor who is defined in Art. 2 lit. c ClinO as the person or institution headquartered or represented in Switzerland that takes responsibility for organising a clinical trial, and in particular for the initiation, management and financing of the trial in Switzerland. Even if no one formally qualifies as a sponsor, e.g. because there never was a full research proposal, the liability norm still applies.[171] In such cases, the sponsor is the individual who would normally be required to assume responsibility.[172] Nevertheless, there is no clear rule in cases where the sponsor is domiciled outside Switzerland.[173]

Importantly, the liability must relate to the characteristics of the research.[174] According to the explanatory report on the preliminary draft legislation, the rule provides for damages, that are causally connected with the participation in the research project, to be recorded. However, in terms of time, all damage caused from the beginning of the research project up to and including its completion would be recorded.[175] Consequently, and in line with the legislative mandate of the federal council stated in Art. 19 para. 1, 2nd sent. HRA, the ClinO and the HRO introduced exemptions from liability, e.g. when damage is attributable to some other health-related intervention which is understood to be standard in guidelines prepared in accordance with internationally accepted quality criteria (Art. 10 ClinO para. 1 lit.

[169] For further information Swissmedic publishes an application establishment license for medicinal products or TP/GT/GMO (Swissmedic 2019a).

[170] Bollag et al. (2016), par. 50; Schroeder de Castro Lopes and Schallnau (2019), p. 60; further Fellmann (2015a).

[171] Bollag et al. (2016), S. N. 53.

[172] Fellmann (2015b), pp. 321 et seq.

[173] Bollag et al. (2016), par. 54.

[174] Schroeder de Castro Lopes and Schallnau (2019), p. 61.

[175] Explanatory Report Pre-Draft HRA, pp. 85, 86.

d). The exceptions to liability in the HRO are limited to "minor damage", which is only temporary and does not go beyond what can be expected according to the state of the art (Art. 12 HRO).

Pursuant to Art. 19 para. 2 HRA, in conjunction with the general provisions of the Swiss Code of Obligations,[176] compensation claims become statute-barred 3 years after the injured party becomes aware of the damage, but no later than 10 years after the completion of the research project. This rule has two exceptions: Firstly, Art. 19 para. 2 HRA confers the competence upon the Federal Council (the Swiss Government) to specify a longer prescriptive period for particular research areas; secondly, the public law of the cantons (the swiss states), in addition to the federal civil law, provides for state liability laws for public research institutions, e.g. stem cell research at a cantonal university hospital.[177]

Besides the liability claims resulting from the HRA, the sponsors could be held liable on more general legal grounds, for example, on the basis of general tort law or contractual liability. In contrast to Art. 19 HRA, however, evidence of fault is required.

5.3.3 Market Placement

Market placement describes the ability to place a product on the market, either to be used by a patient or another end-user.[178] The most relevant legislation regulating such access is the Therapeutic Product Act (TPA) and its related ordinances. As already mentioned above, the TPA does partly apply to transplant products (as which human iPSCs qualify) based on Art. 49 para. 1 Transplantation Act. The TPA further covers gene therapy, insofar as it directly relates to therapeutic products (Art. 2 para 1 lit. c TPA).

Before a ready-to-use medicinal product is placed on the market, i.e. distributed and dispensed (Art. 4 lit. d TPA), a marketing authorisation (MA) granted by Swissmedic is required (Art. 9 para. 1 TPA). There are several exceptions provided in Art. 9 para. 2 TPA. The authorization of gene therapy products and other transplant products requires the applicant to submit a complete dossier according to the ICH Common Technical Document (CTD) M4 guideline.[179] These involve small quantities of medical products according to a specific preparation and intended

[176] The Swiss Code of Obligations contains the civil law of obligations and contract law. The Code of Obligations is contained in part five of the Swiss Civil Code, also officially called the Federal Act on the Amendment of the Swiss Civil Code.

[177] Cf. e.g. Canton de Vaud: Loi sur la responsabilité de l'Etat, des Communes et de leurs agents (LRAECA) du 16 Mai 1961, and: Loi sur la santé publique (LSP) du 29 mai 1985, art. 25 Recherche biomédicale avec des personnes. The CHUV, the main hospital in Lausanne, is one of the central places in biomedicinal research in Switzerland.

[178] Schroeder de Castro Lopes and Schallnau (2019), p. 70.

[179] For further information see Marti (2015), p. 143 et seq.

for a small number of persons (lit. a, b, c). Moreover, medicinal products intended for clinical trials and those that cannot be standardised are exempted (lit. d and e).[180] However, according to Art. 2 para. 2 lit. b Ordinance for Therapeutic Products,[181] transplant products, and thus human iPSCs, require an MA by Swissmedic in every case.[182] Following Art. 32 Ordinance for Therapeutic Products non-standardisable transplant products whose manufacturing process can be standardised may only be placed on the market if the manufacturing process has been authorised by Swissmedic.

Art. 10 revTPA sets out the conditions for granting the MA. Thus, the applicant must

- prove that the medicinal product is of high quality, safe and effective.
- be a holder of an authorisation to manufacture, import, or conduct wholesale trade issued by the competent authority.
- have a registered address, registered office or a branch office in Switzerland.

More specifically, the first aspect includes the following: the quality requirements demand, on the one hand, compliance with the Good Manufacturing Practice guidelines (GMP guidelines), listed in Annex 1 of the ordinance of the MPLO. On the other hand, the pharmacopeia, the official compendium of medicines which includes binding quality regulations, must be met. In order to evaluate the safety of a medicinal product, a risk-benefit analysis based on preclinical and clinical study results, as well as adverse event documentation and reporting, is conducted.

A request for a marketing authorisation needs to be filed in the harmonised format of the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (*ICH*).[183] The application will then be formally checked and subsequently reviewed, focusing on scientific aspects. The applicant then answers a list of relevant questions (LoQ) which will be examined in a second evaluation ending with a preliminary decision. After the applicant submits the (revised) information, an official decision follows. For the centralised procedure,

[180] According to Art. 28. 2 of Regulation EC 1394/2007 of the European Parliament, certain ATMPs which are non-routinely manufactured, but manufactured in healthcare facilities and used under the professional supervision and responsibility of a doctor on a patient, do not require a centralised authorisation. Although in Switzerland no explicit "hospital exemption" exists (Mumme et al. 2020, p. 93), in practice and under certain conditions, medical freedom of therapy can act as a surrogate for a product authorisation in the therapeutic products sector (We thank Dr. iur. et dipl. sc. nat. ETH Stefan Kohler, Partner at VISCHER for his valuable information).

[181] There is no English version, the German title is "(Arzneimittelverordnung, VAM)".

[182] Cf. Federal Office of Public Health (2018b), pp. 5 et seq.

[183] The ICH aims to achieve greater harmonisation worldwide to ensure that safe, effective and high-quality medicines are developed, registered and maintained in the most resource-efficient manner (ICH n.d.).

the processes and application time limits follow the EMA—where applicable. Moreover, different sorts of authorisation procedures and fees apply.[184]

As discussed above, the GTA might be applicable in cases in which human iPS Cells are used in extra-human areas. Thus, in case of uncertainty, the safety requirements of Art. 6 GTA and Art. 10–12 GTA must be complied with. The first article sets out the general principles regarding the release for experimental purposes and their circulation in order to protect human beings, animals, the environment and biological diversity. A federal authorisation is required to release genetically modified organisms for experimental purposes (Art. 11 GTA) and to put them into circulation (Art. 12 GTA).

5.3.4 Patentability

In the context of the legal protection of biotechnological inventions, the basic norm in Swiss Law is Art. 119 FedCst, which includes the prohibition on the commercialisation of human reproductive material and on products obtained from embryos (para. 2 lit. e). As a state associated to the EU through several treaties and as a member state of the Convention on the Grant of European Patents (European Patent Convention) of October 1973, Switzerland is interested in harmonised rules to increase legal certainty.[185] In 1998, the parliament accepted a motion[186] demanding the adaptation of the Federal Act on Patents for Inventions (Patents Act, PatA) of 25 June 1954 to the Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions (hereafter "EU Directive 1998"). With the introduction of the Stem Cell Research Act in 2003, patent prohibitions in relation to stem cells were included in the PatA. In 2007, a comprehensive amendment of the Patents Act was adopted.[187] In December 2007, the Implementing Regulations to the Convention on the Grant of European Patents (AO EPÜ 2000) came into force in Switzerland setting rules for patentability at the European Patent Office.

In accordance with the EU Directive 1998, as well as Art. 53 lit. a European Patent Convention, the PatA excludes inventions from patentability if they are contrary to public policy or morality by way of a general clause.[188] As such, the human body at all stages of its formation and development, including the embryo, is not patentable (Art. 1*a* para. 1 PatA, Art. 5 para. 1 EC-Directive). Thus, overriding legal and ethical values are taken into account when granting patents; the legal

[184] Schroeder de Castro Lopes and Schallnau (2019), pp. 82–85, see pp. 85 et seq. for further information about the different forms of authorisation procedures.

[185] Cf. Kohler (2006), p. 454, including further details on the issue.

[186] Motion Leumann.

[187] Schweizer (2009), p. 74.

[188] Dederer (2009), p. 21 with further remarks; Calame and Thouvenin (2006), par. 12.

specification by reference to the human body and the embryo serves authorities as an important guideline for the individual case.[189] Although elements of the human body in their natural environment are not patentable, an element of the human body is patentable if it is produced by means of a technological process (Art. 1*a* para. 2 PatA). As such (unmodified) human cells, above all germ cells which are protected from trade by Art. 119 lit. e FedCst, are not patentable. Human iPSCs itself however are developed in the laboratory with technological means. As they are modified somatic cells, they are generally patentable. Nevertheless, Art. 2 PatA addresses important constitutional concerns about the protection of human dignity, human integrity and identity[190] and excludes inventions in contrary of human dignity from patentability (para. 1). Further, the article concretises the general clause in an exemplary list of exclusions from patentability. The article thereby includes prohibitions from the European Patent Convention, the EU-Directive 1998, the AO EPÜ 2000 (Art. 28 and 29) as well as from the RMA and StRA (para. 1 lit. a–g).[191] Art. 2 para. 2 PatA excludes methods of surgery, therapy and diagnostics from patent protection. In this way, the legislator wants to ensure the greatest possible freedom of access to procedures that affect human and animal health.[192]

Art. 2 PatA Exclusion from Patentability

1. Inventions whose exploitation is contrary to human dignity or that disregard the integrity of living organisms or that are in any other way contrary to public policy or morality are not patentable. In particular, no patent may be granted for:
   a. processes for cloning human beings and the clones obtained thereby;
   b. processes for forming hybrid organisms by using human germ cells, human totipotent cells or human embryonic stem cells and the entities obtained thereby;
   c. processes of parthenogenesis by using human germinal material and the parthenogenetic entities obtained thereby;
   d. processes for modifying the germ line genetic identity of human beings and the germ line cells obtained thereby;
   e. unmodified human embryonic stem cells and stem cell lines;
   f. the use of human embryos for non-medical purposes;
   g. processes for modifying the genetic identity of animals which are likely to cause them suffering without being justified by overriding interests worthy of protection, and also animals resulting from such processes.
2. Also excluded from patentability are:
   a. methods for treatment by surgery or therapy and diagnostic methods practised on the human or animal body;

[189] Calame (2007), p. 771.
[190] Cf. Art. 7 FedCst.
[191] Thomsen (2019), p. 78.
[192] Schweizer (2009), p. 83.

b. plant varieties and animal varieties or essentially biological processes for the production of plants or animals; however, subject to the reservation of paragraph 1, microbiological or other technical processes and the products obtained thereby as well as inventions that concern plants or animals are patentable provided that their application is not technically confined to a single plant or animal variety.

More concrete, all processes for modifying the human germ line are excluded from patentability by para. 1 lit. d. Whereas somatic gene therapy is not covered by lit. d,[193] Art. 2 para. 2 lit. a PatA is restricting.[194] However, since para. 2 lit. a, only excludes therapy *on* humans, somatic gene therapy *in vivo,* but not *in vitro* seems to be affected.[195] Art. 2 para. 1 lit. e prohibits the patentability of unmodified embryonic stem cells and stem cell lines, other pluripotent stem cells, as human iPSCs, are not covered according to the wording. Art. 2 lit. f prohibits the use of human embryos for commercial, industrial and scientific purposes.[196]

With regard to the propagation of biological material, Art. 8a para. 2 PatA makes it clear that the importance of the patent is even greater for products obtained by propagation of this biological material and which demonstrate the same characteristics. The legislator thereby wants to extend patent protection to all subsequent generations and thus prevent patent protection being undermined.[197] This concept extends the protection of the process.[198] There are, however, some exceptions in Art. 9 PatA to these extensions: the research privilege introduced in Art. 9 para. 1 PatA is particularly relevant. This broadly defined privilege excludes any scientific research, even commercially oriented, on the subject matter of the patented invention from the effects of patent law.[199] The legislator thus wants to guarantee freedom of research by ensuring that basic and applied research is not inhibited by patents. The research privilege is completed by the licence claim for research tools and diagnostics in Art. 40*b* and 40*c* PatA. According to Art. 40*b* PatA, every researcher is entitled to a non-exclusive mandatory license for the use of biotechnological research tools.

[193] Heinrich (2018), par. 36; Thomsen (2019), par. 17.

[194] Heinrich (2018), par. 36.

[195] Calame (2003), p. 86; Heinrich (2018), par. 58.

[196] Cf. ECJ, C-34/10, 18 October 2011 (Grand Chamber), ECLI:EU:C:2011:669.

[197] Federal Council's Dispatch PatA, p. 66.

[198] Process patents protect the respective manufacturing process and the direct products of this process (Art. 8a (1) and 8b PAtA).

[199] Federal Council's Dispatch PatA, pp. 70 et seq.

5.4 Human Germ Line Intervention Through Genome Editing

The findings of iPSCs by Takahashi/Yamanaka in 2006 were not only important regarding somatic gene/cell therapy, but also impacted the discussions on human germ line interventions. The following section aims to broaden the viewpoint from human iPSCs in the somatic context and reflects on the requirements of Swiss law regarding genome editing and germline intervention.

Since 2015, human germ line interventions through genome editing have been discussed in the international context and several statements have followed.[200] Germ line interventions through genome editing hold the prospect of curing serious, hereditary diseases and preventing disabilities, among other things. For example, both parents may suffer from a monogenic disease such as cystic fibrosis[201] and wish to have a child together. In this case, PGD would not be a possible alternative, as all the embryos of this couple would be affected by the disease.[202] In comparison to conventional methods, CRISPR/Cas9 nowadays allows for more precise, simpler and less expensive interventions.[203] Whereas in 2015 the work by Liang et. al., examining CRISPR/Cas9-meditated genome editing in human embryos, revealed several off-target mutations and made clear that the technology is still in its beginnings,[204] further research over the following years reported success in the repair of genetic damage.[205] At the First International Summit on Human Gene Editing in 2015, researchers were arguing against the demand of several scientists and ethics committees for a moratorium on germ line interventions: interventions should continue for basic research; however, they opposed the application of the technique, e.g., with regard to the creation of designer babies.[206] This fundamental idea was heavily strained in November 2018, after the revelation by He Jiankui of his experiments with twin girls. Despite the presentation of the technical possibilities, the research broke the, by then, untouched taboo: to change the heritable genome of a human being mainly for purposes which could, arguably, characterised as enhancement purposes.[207] The Organizing Committee of the Second International Summit on Human Gene Editing, which took place in 2018, characterised the procedure as irresponsible and contrary to international norms. The committee concluded that the

[200] Deuring (2020), p. 13.

[201] Cystic fibrosis is a congenital metabolic disease. It is caused by a change in the cystic fibrosis gene, the CFTR gene (Mukoviszidose e.V. [2020]).

[202] German Ethics Council (2019), pp. 179 et seqq.

[203] Nationale Ethikkommission im Bereich der Humanmedizin (2016), p. 2. See e.g. Hockemeyer and Jaenisch (2016); Kang et al. (2016); Wilbie, Walther and Mastrobattista (2019).

[204] Liang et al. (2015); Nationale Akademie der Wissenschaften Leopoldina et al. (2015), p. 11.

[205] Sprecher (2017), p. 1470.

[206] The National Academies of Sciences, Engineering, and Medicine (2015).

[207] More information on this experimentation: Lang and Griessler (2019), passim.

scientific understanding, technical requirements and risks are too great, and thus they continued to believe that proceeding with any clinical use was irresponsible at this time.[208]

The rapid development of molecular biological instruments, the applications of which allegedly brought about the birth of genome edited twins in November 2018, increasingly highlights the possibility of intervention in the human germ line.[209] Increasingly, discussions arise as to the extent to which a categorical rejection of germ line intervention can be maintained.[210] The ISSCR holds in its Guidelines (2021): "Recommendation 3.4.8.3.4: Regulators, research funders, and academic and medical societies should seek to prevent the premature or unethical clinical uses of heritable genome editing unless and until the safety, ethical, and societal issues associated with the clinical use of heritable genome editing are resolved." In other words, a broad discussion seems necessary and urgent. In the following section, we first attempt to present the current legal situation as to germ line interventions in Switzerland and then discuss certain imminent developments.[211]

5.4.1 Forms of Germ Line Interventions

Diseases that are based on genetic mutations can, *inter alia,* be treated or even prevented through genetic correction in the germ line, so-called germ line interventions. In theory, germ line interventions have several different areas of application. In the foreground are treatments of monogenetic predispositions to diseases; in addition, prophylactic interventions might be used to reduce the risk of diseases. Moreover, germ line intervention might theoretically be used for enhancement purposes, i.e. by direct modification or improvement of non-pathological characteristics.[212] All of these interventions aim to define desired genetic characteristics in all cells of an individuum from the beginning, and imply that the modifications would be transferred to future generations.[213] An intervention in the reproductive or genetic material can thus be conducted on the embryo, directly in the germ stem cells, or on stem cells prior to the development of germ cells.[214] These three forms are examined below:

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[208] The National Academies of Sciences, Engineering, and Medicine (2018); on this critically Raposo (2019a).

[209] Cf. German Ethics Council (2019), p. 48.

[210] Comité Consultatif National d'Éthique pour les sciences de la vie et de la santé, German Ethics Council, Nuffield Council on Bioethics (2020), p. 4; For example, Rütsche (2010); Cf. Rütsche (2017), pp. 244 et seq.; German Ethics Council (2019), e.g., pp. 35, 44, 232.

[211] For the latter, see also the two informative and relevant contributions by Sprecher (2017, 2020) which deal with the subject in detail.

[212] Cf. Schöne-Seifert and Stroop (2015), p. 2.

[213] German Ethics Council (2019), p. 65.

[214] The German Ethics Council explained these forms in great detail and examined their implications in their valuable statement "Intervening in the Human Germ Line" of 2019.

Firstly, genetic modifications on the germ line could already take place directly on the embryo at an early stage (pronuclear stage or one-cell-stage).[215] However, if the embryonic genome is modified in vitro, there is a risk of mosaic formation. The resulting organism might consist partly of modified and partly of unmodified cells, as the genome editing tools may not reach all later cells of the embryo.[216] Although mosaic formation occurs naturally, its consequences cannot be conclusively determined. One possibility to reduce the risk is promised by developments of the CRISPR/Cas method.[217] The development of mosaic structures could be prevented, secondly, through interventions directly in the germ cells, if the intervention was terminated prior to the first cell cleavage.[218] Despite its advantages, the structure of mature germ cells and their genomes inherit certain challenges for correcting germ cells with precise genome engineering.[219] Furthermore, the interferences cannot be verified without destroying the germ cells.[220] As it is currently impossible to know which germ cell encompasses a genetic defect, a genetic modification to treat this defect might always change the genetic structure of a "healthy" germ cell.[221] The most secure option to ensure that an intervention leads to the desired objective and that no adverse side effects occur, would be, thirdly, to conduct the modification in stem cells that allow for analysis prior to the generation of an embryo. This could be done either by producing new germ cells using as a basis germ stem cells or iPSCs, or by injecting genetically modified (embryonic) stem cells into a decored germ cell,[222] or by combining it with an unfunctional embryo.[223] The basis of all this research is an in-depth knowledge of human embryonic development, especially of the blastula gastrulation as the most important part of life evolution.[224] Increasingly, models for embryonic development research, so-called blastoids, are being created and developed, not least because the in utero research on embryos is only permitted to a very limited extent.[225] The ISSRC Guidelines define stem cell-based embryo models as "advances in cellular engineering make possible the assembly,

[215] Cf. Cantz (2022), Chap. 2, Sect. 2.4 (this volume).

[216] Le Page (2017) with reference to Tang et al. (2017).

[217] German Ethics Council (2019), p. 68 with reference to Tu et al. (2017).

[218] German Ethics Council (2019), p. 68.

[219] Cantz (2022), Chap. 2, Sect. 2.3 (this volume) with reference to Mulder et al. (2016); German Ethics Council (2019), p. 68.

[220] German Ethics Council (2019), p. 68.

[221] German Ethics Council (2019), pp. 68 et seq.

[222] German Ethics Council (2019), p. 70 with reference to Araki and Ishii (2014) and Wakayama et al. (1999).

[223] German Ethics Council (2019), p. 70 with reference to Li et al. (2017).

[224] See e.g. Tyser et al. (2021).

[225] Liu et al. (2021); Zheng and Fu (2021); Kagawa et al. (2021). The researcher Nicolas Rivron from Vienna reports in the news of the Austrian Academy of Sciences (ÖAW) dated 2 December 2021, how embryo models pave the way for new models of birth control and improvements in assisted reproduction.

differentiation, aggregation, or re-association of cell populations in a manner that models or recapitulates key stages of embryonic development".[226]

A serious problem with current embryo research is the universally accepted rule that e.g. supernumerary embryos originating from assisted reproductive medicine may not be developed even in vitro for more than fourteen days. The 14-day limit, first articulated in 1984 by the Warnock committee of the U. K. Human Fertilisation and Embryology Authority, is widely accepted by researchers in the human stem cell and fertility fields. It recognizes the significant biological distinctions between the earliest human embryos, which have not yet established even the most rudimentary rostral and caudal orientation (the primitive streak), and an embryo that has begun to initiate organogenesis.[227] The ISSCR notes that it is currently not technically feasible to culture human embryos beyond formation of a primitive streak or 14 days post-fertilization. However, culture systems are evolving, making this a possibility in the near future. It is therefore necessary to lead public scientific conversations on the scientific significance as well as the societal and ethical issues raised by allowing such research.[228]

5.4.2 General Legal Framework

As seen above, the Swiss federal constitution strictly prohibits any interference with the genetic material of human reproductive cells and embryos in Art. 119 para. 1 lit. a FedCst.

Art. 119 FedCst Reproductive Medicine and Gene Technology Involving Human Beings

1. Human beings shall be *protected against the misuse of reproductive medicine and gene technology.*
2. The Confederation shall legislate on the use of human reproductive and genetic material. In doing so, it shall ensure the protection of human dignity, privacy and the family and shall adhere in particular to the following principles:
   a. All forms of cloning and *interference with the genetic material of human reproductive cells and embryos are unlawful.*

   . . .

[226] ISSCR Guidelines (2021), page Embryo Models <https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinicaltranslation/key-topics/embryo-models>.

[227] The U.S. NAS guidelines prohibit the mixing of cells of any nature with the pre-streak embryo. This restriction excludes a number of experiments considered standard in animal embryology, including cell aggregation studies to investigate the segregation of primitive embryonic blastomeres into inner cell mass and trophectoderm.

[228] ISSCR Guidelines (2021), page Culture of Human Embryos <https://www.isscr.org/policy/guidelines-for-stem-cellresearch-and-clinical-translation/key-topics/culture-of-human-embryos>

The prohibition encompasses the entire embryonic phase, both in vitro and embryos in the mothers' womb,[229] as well as precursor cells.[230] This is independent of the treatment objective, i.e. whether the interference is conducted for therapeutic reasons, e.g. procreation assistance or treatments of monogenetic predispositions to diseases, or for enhancement.[231] In this respect, "interferences" or "interventions" are legal rather than biological terms and need to be understood as intended changes to the genetic material of reproductive or embryonic genetic material.[232] These changes either activate or deactivate existing genes or introduce new genes into the genome. Hence, one may infer a fundamental right to non-artificially modified genetic material, which does not only protect the integrity of a person, but also that of their heirs.[233] The prohibition is concretised in the Stem Cell Research Act (Art. 3 para. 1 lit. b StRA) and the Reproductive Medicine Act (RMA) penalises a lack of compliance with the prohibition with a prison sentence of up to 3 years (Art. 35 para. 1 RMA).

Nevertheless, certain exceptions do exist: As mentioned above,[234] somatic gene therapy, which modifies the genetic material without passing it on to further generations, is not prohibited.[235] Additionally, Art. 119 para. 2 lit. a FedCst does not prohibit observational, clinical examinations, as well as the mere examination of embryonic cells in the context of prenatal diagnostics (PND) or eventually of a PGD.[236] Art. 5a RMA permits since 2017 under strict conditions a prenatal diagnostics of gametes and embryos in vitro.[237] Also not covered are medical measures, e.g. a chemo or radiation therapy that inescapably leads to a change in the genetic material of germ cells, such as gametes (Art. 35 para. 3 RMA).[238]

The idea of Art. 119 para. 2 FedCst is reflected in international treaties, such as the Biomedicine Convention and its rule on germ line interventions:

> **Article 13 Biomedicine Convention. Interventions on the Human Genome**
> An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.

[229] Belser and Molinari (2015c), par. 16; Reusser and Schweizer (2014b); Schweizer (1996).

[230] *Pro memoria*, all methods are prohibited which are not aimed at the health and integrity of the child, but at a positive eugenic selection of embryos or germ material, Rütsche (2009), pp. 274 et seqq., 427 et seqq.; cf. Art. 33 RMA *e contrario*.

[231] Federal Council Dispatch RMA, p. 283.

[232] Sprecher (2017), p. 1471.

[233] Reusser and Schweizer (2014b), par. 23.

[234] Cf. Sect. 5.2.1.1.

[235] Belser and Molinari (2015c), par. 29.

[236] Staub (2019); Aubert (2003), par. 14.

[237] Junod, Wunder and Hurst (2018), par. 11 et seq., 25 et seq.; Staub D (2019), passim; Boillet (2021), par. 43.

[238] Reusser and Schweizer (2014b), par. 25.

In comparison with the prohibition in the constitution, the Biomedicine Convention is less restrictive, as it allows interventions which aim to modify genetic characteristics for preventive, diagnostic or therapeutic purposes. According to the explanatory report on the Biomedicine Convention, "as long as somatic cell gene therapy is currently at the research stage, its application can be allowed only if it complies with the standards of protection provided in the Convention."[239] Like the Swiss regulation, Art. 13 of the Biomedicine Convention "does not rule out interventions for a somatic purpose that might have unwanted side-effects on the germ cell line", e.g. certain cancer treatments by radiotherapy with effects on the reproductive system of the patient.[240]

The strictness of the prohibition raises the question of the underlying protective interest of the prohibitions. There is an ongoing discussion about the reasoning of the discussion. The *fundamental-categorical argumentation* is based primarily on human dignity and objects to a "human being made to measure".[241] Whereas the so-called *slippery-slope argument* emphasises the blurred distinction between therapeutic-preventive and enhancement interventions,[242] the *technical-pragmatic view* gives the lack of maturity of the technology and the incalculable risks associated with it as reasons.[243] In contrast to the background of the German prohibition on germ line interventions, where safety concerns were paramount and fundamental-categorical arguments were not further specified,[244] in Switzerland the primary interest in the first years was, according to the parliamentary debate in 1990/1991, to prevent human breeding and positive eugenics (fundamental-categorical argument).[245] Although the objection to a "tailor-made human being" does in principle not exclude therapeutic germ-line interventions, germ line therapy was banned because it was feared that it could be misused for perfection or enhancement (slippery-slope argument).[246] Accordingly, the Federal Government (Federal Council) argued in the dispatch of the RMA that the nascent human being shall be

[239] Cf. Explanatory Report Biomedicine Convention; Radau (2006), pp. 213 et seqq.

[240] Cf. Explanatory Report Biomedicine Convention; The Council of Europe's Committee on Bioethics examines the practical and legal implications of Art. 13 and whether clarifications or amendments are required (CoE Strategic Action Plan 2020–2025, p. 9).

[241] Federal Dispatch RMA, p. 281; cf. Federal Dispatch Biomedicine Convention, pp. 310 et seq.; Rütsche (2010), p. 305; Sprecher (2020), p. 303. For additional informations on the concept and scope of the fundamental right to respect and protect human dignity (Art 7 FedCst) see BGE 142 IV 77 cons. 4.1, 82 et seqq.; 119 Ia 460 cons. 12c-12e, 501 et seqq.

[242] Federal Dispatch RMA, p. 282; cf. Federal Dispatch Biomedicine Convention, pp. 310 et seq.; Rütsche (2010), p. 305; in conjunction with Genome Editing: Nationale Ethikkommission im Bereich der Humanmedizin (2016), p. 2.

[243] Reich et al. (2015), p. 12.

[244] Advena-Regnery et al. (2018), p. 283; Günther (2014), par. 3.

[245] Rütsche (2010), p. 305.

[246] Votum Piller, AB 1990, p. 488; Expertenkommission Humangenetik und Reproduktionsmedizin (1989); Schweizer (1996), par. 57.

protected against manipulation and experiments, the consequences of which cannot be assessed for them or for future generations.[247]

5.4.3 Further Legal Considerations

5.4.3.1 Germ Line Interventions on Embryos

As mentioned above, interventions in the genomes of embryos are one form of human germ line intervention.

Art. 119 para. 2 lit. a FedCst explicitly prohibits interventions in the genetic material of embryos, highlighting their special status. However, the rights of the embryo itself have not been fully clarified in Switzerland. Opinions vary between the attribution of an individual right to life and a minority that assumes that the embryo in vitro does not have any right to life.[248] The federal legislator chooses the middle course and assumes that the embryo enjoys—as a human being—a certain constitutional status providing protection of its dignity as a human being.[249] At least partially, a certain protection of health and life is accorded to it.[250] Although embryos and fetuses in vivo and in vitro do not have per se fundamental rights under Swiss law,[251] a certain protection of human integrity already exists in the prenatal phase.[252]

Similarly, research with embryos is not systematically and comprehensively regulated, but is rather fragmented and partly incoherent.[253] Art. 119 FedCst does not aim at imposing an absolute prohibition on research with human embryos, but rather establishes certain limitations to protect the specific genome of a singular human being.[254] In general, no research that is harmful to the health or life of the embryo or fetus, or which exploits it in any other way, may be carried out on living embryos (in vitro or in utero) as long as they are conserved and destined to induce a pregnancy and thus still have developmental chances (cf. Art. 119 para. 2 FedCst, cf. Art. 17 and Art. 29 et seq. RMA, Art. 3 para. 2 lit. a StRA confirms this

[247] Cf. Federal Dispatch RMA.

[248] Federal Council's Dispatch EFG, p. 1187; cf. Nationale Ethikkommission im Bereich der Humanmedizin (2016), pp. 2 et seq.; Hertig Randall and Marquis (2021), Art. 10 para. 15 FedCst; Reusser and Schweizer (2014b), par. 16 with further information; Rütsche (2009), p. 230 et seqq.; Augustin (2001), p. 174.

[249] Federal Dispatch RMA, pp. 5946 et seq.; Federal Council's Dispatch EFG, pp. 1186 et seqq.

[250] Sprecher (2017), p. 1478.

[251] Sprecher (2017), p. 1478; Rütsche (2015), par. 16 et seq.; cf. Manaï (2009), par. 62.

[252] Rütsche (2009), par. 68; Reusser and Schweizer (2014b), par. 16 et seqq.; Belser and Molinari (2015c), par. 15.

[253] Nationale Ethikkommission im Bereich der Humanmedizin (2016), p. 4.

[254] Gruber and Sommer (2019), p. 287 et seqq.

explicitly).[255] Further, the donation or adoption of surplus embryos (Art. 119 para. 2 lit. d FedCst), all forms of ectogenesis of embryos, and the use of non-human cells and tissues in all procreation procedures are prohibited. Nevertheless, strictly monitored research on embryos in vivo is allowed within the limiting framework of the Swiss constitution and the HRA.[256]

5.4.3.2 Germ Line Interventions on Germ Cells

As explained above, the risks of mosaic formation resulting from modifications in the embryo itself could be reduced through direct interventions in germ cells.

According to the general legal framework, presented above, interventions in the genetic material of reproductive cells, i.e. germ cells, are prohibited by Art. 119 para. 2 lit. a FedCst. The modification of gametes is addressed again in the Reproductive Medicine Act (RMA), which specifies the conditions under which techniques of medically assisted reproduction may be used in humans (Art. 1 para. 1 RMA). In addition to the prohibition on germ line intervention, Art. 35 para. 2 RMA prohibits the use of artificially modified germ cells for impregnation, i.e. causing a sperm cell to penetrate into the cytoplasm of an ovum, in particular by insemination, gamete transfer or in vitro fertilisation (Art. 2 lit. g RMA).[257]

If no genetic modification is conducted on the germ cell, research is generally permitted. As opposed to the research prohibition relating to embryos in vitro, *de lege lata,* no such provision exists. However, Art. 32 RMA covers the misuse of reproductive material. Firstly, it penalises any usage of reproductive material obtained from an embryo or foetus in order to bring about impregnation or further development of an embryo. Moreover, the article provides for a penalty for selling or purchasing human reproductive material, or material derived from embryos or foetuses. Despite not being mentioned in Art. 119 para. 2 lit. d FedCst, ovaria donations are prohibited in Art. 4 RMA, whereas sperm cell donations are permitted (Art. 18 et seqq. RMA).[258]

[255] This was also made clear by the Federal Supreme Court in BGE 119 Ia 500, E. 12e, 502.; as already mentioned in Sect. 5.3, today's allowance to create 12 surplus embryos during PID seems inconsistent with this strict set of prohibitions. In addition, the prohibition on research on embryos in vitro stands in contrast to the permission to research on ESCs, as in the latter case embryos are destroyed.

[256] Sprecher (2017), p. 1479; for a stimulating discussion on the question whether genome editing should be researched using CRISPR/Cas on human embryos see Pro: Kipke et al. (2017), pp. 249–252; Rütsche (2017).

[257] Federal Council Dispatch RMA, p. 283.

[258] In 2013/2014 there were several attempts to revise Art. 4 RMA arguing that the provision violates the fundamental right to personal liberty (Art. 10 FedCst) and discriminates against women. For further elaborations, see the expert report Büchler (2013).

5.4.3.3 Germ Line Interventions on Stem Cells

5.4.3.3.1 Embryonic Stem Cells Used for Germ Line Intervention

Germ line interventions can be conducted by injecting genetically modified ESCs in decored ova or by combining them with nonfunctional embryos. Technically, at least, there are three possible sources of ESCs: firstly, the creation of embryos[259] in vitro for research purposes, secondly, the use of surplus embryos from an IVF to create embryonic cell lines and, thirdly, the use of imported embryonic cell lines.

The creation of embryos in vitro for research purposes is misleadingly called "therapeutic cloning" and is prohibited given the prohibition on all forms of cloning, independent of its purpose and technique used (Art. 119 para. 2 lit. a FedCst, Art. 1 Additional Protocol Biomedicine Convention regarding Cloning,[260] Art. 3 para. 1 lit. a StRA, Art. 29 para. 1 and 35 RMA).[261] The prohibition on therapeutic cloning can, at best, be justified by the fact that it is only a small step away from reproductive cloning.[262] According to certain ethical or legal arguments, the creation of embryos purely for research purposes entails the complete instrumentalisation of human life; for others, it makes no difference whether the embryo is created for research or for in vitro fertilisation.[263] In Switzerland, generating ESCs out of surplus embryos is permitted (Art. 3 para. 2 lit. a StRA). However, research purposes other than the generation of ESCs, e.g. solely in developmental biology, are prohibited (Art. 3 para. 2 lit. a, Art. 5 and 8 StRA). In this context, "surplus" embryos are embryos produced in the course of an in vitro fertilisation (IVF), but which cannot be used to achieve a pregnancy and would thus be incapable of survival (Art. 2 lit. b StRA).[264] Whereas extraction was severely restricted for a long time, the possibilities expanded with the latest revision of Art. 119 FedCst and the Reproductive Medicine Act (RMA). For several years, the regulation in the RMA aimed at not deriving any surplus embryos.[265] Since the introduction of PGD in 2017, however, the rule was extended. Currently, the number of impregnated ova developed into embryos outside a woman's body in one treatment cycle must not be greater than required and must not exceed a maximum of 12, according to Art. 17 para. 1 RMA. With the written consent of the relevant couple (Art. 5 StRA), the

[259] While deriving ESCs from an embryo, the embryo is destroyed.

[260] Note that the Biomedicine Convention implicitly allows cloning for therapeutic, preventive and diagnostical reasons in Art. 13; see also Reusser and Schweizer (2014b), par. 28 et seq. For technical details on cloning see: National Human Genome Research Institute, Cloning Fact Sheet (August 15, 2020).

[261] Reusser and Schweizer (2014b), par. 22; Schwander (2002), pp. 214 et seq.; Müller et al. (2003), pp. 147 et seqq.; Viaccoz (2013), p. 661; Belser and Molinari (2015c), par. 25; Boillet (2021), par. 30 et seqq.

[262] Augustin (2001), p. 176.

[263] Augustin (2001), p. 175.

[264] Federal Office of Public Health (2018e).

[265] Cf. Art. 119 para. 2 lit. c FedCst; Art. 17 para. 1 RMA.

surplus embryos can be used for research purposes.[266] The extension of the RMA, combined with the limited usability of surplus embryos, leads to surplus embryos generally having to be destroyed. Finally, ECSs could be imported. In 2001, the Swiss National Fond supported a research project that included imported embryonic stem cells. This initiated a public debate that subsequently led to the StRA.[267] Under the current law, import into Switzerland is permitted if no surplus embryos exist. Moreover, an authorisation is required (Art. 15 StRA) from the Federal Office of Public Health (FOPH), and their storage needs to be reported (Art. 16 StRA).

The StRA is the main legal source for research with ESCs in general. According to Art. 12 lit. A StRA, a research project involving ESCs must serve the purpose to gain important insights in terms of detection, treatment or prevention of serious diseases or development of human biology. Research on surplus embryos (and the storage for research purposes) is thus permitted under strict licensing requirements (Art. 7–10 StRA), and subject to the consent of the couple concerned (informed consent, Art. 5 StRA). A research project involving ESCs requires the approval of the responsible ethics committee (Art. 11 StRA) and the authorisation of the FOPH. Derivation will be authorised if the project has been approved by the respective ethics committee, if no suitable ESCs are available in the county, and only if the required amount of ESCs is used. Moreover, the technical and operational requirements must be met (Art. 7 StRA).[268] The StRA also applies after the extraction of ESCs from surplus embryos resulting from the process of IVF and regulates the storage of ESCs.[269] Storing is allowed for research purposes if the research is authorised (cf. Art. 7 StRA), if storage is absolutely necessary and if the technical and operational requirements are met (Art. 10 StRA). For transplantation purposes, however, the surplus embryo can be kept alive for a maximum of 7 days (Art. 37 Transplantation Act).

Regarding the prohibition on germ line intervention, the Federal Council elaborated, in its dispatch to the StRA in 2002 in relation to Art. 2 para. 1 lit. b, that further clarification is required as to modifying interventions in embryos and ESCs: "As such, it is forbidden to obtain and use stem cells from embryos that have been modified accordingly. On the other hand, the alteration of the genetic material of embryonic stem cells is not prohibited because such an alteration – embryonic stem cells are pluripotent and not totipotent [. . .] – cannot be passed on."[270] Notwith-

[266] Embryo donation is prohibited (cf. Belser and Molinari 2015b, c, par. 42). However, cells and tissues derived from embryos might be transplanted after complete information and agreement of both parents (cf. Art. 37 et seqq. Transplantation Act). Concerning the use of surplus embryos for research purposes see Savioz-Viaccoz (2021), pp. 498 et seqq.

[267] Cf. Nationale Ethikkommission im Bereich der Humanmedizin (2001) and SRF (2018).

[268] For further information and the required documentation see Federal Office of Public Health (2018c).

[269] Federal Office of Public Health (2018d).

[270] Translated from German to English from Federal Dispatch StRA, p. 1243.

standing that view, however, the entire embryonic phase is covered by the scope of the ban on germ line intervention laid down in Art. 119 para. 2 lit. a FedCst.[271] Accordingly, the Federal Council had stated in the dispatch to the RMA in 1996, that "it does not matter if the embryonic cell is a totipotent cell or not. This is in line with the wording of the Federal Constitution and takes into account the fact that the question of how long embryonic cells are totipotent has not been clarified. The embryo is so vulnerable that it must be comprehensively protected from genetic manipulation."[272] In addition, Art. 35 para. 1 RMA explicitly penalises genetic modifications of embryonic cells, which include ESCs; and Art. 25 para. 2 RMA penalises the use of genetically modified reproductive cells for an embryonic development. Besides, current technology allows for heritable genetic modifications in germ cells, supporting the argument that linking the permission for genetic modifications to the totipotency or pluripotency of a cell is no longer adequate.

5.4.3.3.2 Induced Pluripotent Stem Cells Used for Germ Line Intervention

As described above, an alternative strategy for achieving hereditary genomic alterations could be to engineer cells with the desired variants before causing them to become sperm or egg cells. The starting point for this could be the cultivation of stem cells, e.g. iPSCs which are undifferentiated precursor cells for gametes.[273] In 2011/2012, Hayashi et al., for the first time, managed to generate functioning germ cells out of iPSCs in mice using a combined in vitro-in vivo approach.[274] Through fertilisation with a natural sperm cell, healthy progeny could be bred.[275] To date, it has already been possible to create germ line cell stages from human cells, but a mature germ cell has not yet been developed.[276] The long duration and complexity of the process of germ line cell development in humans presents a challenge.[277] Thus, it remains unclear when and how functional gametes could be obtained. Besides creating these artificial gametes only in order to use them as cellular transplant for the treatment of infertility,[278] germ line modifications can be conducted by modifying the iPSCs prior to their redifferentiation into germ cells. As artificial gametes will be legally examined in the following section (Sect.

[271] Reusser and Schweizer (2014b), p. 23; cf. Belser and Molinari (2015c), par. 29; Boillet (2021), par. 30 and 45; Savioz-Viaccoz (2021), pp. 446 et seqq.

[272] Federal Dispatch RMA, pp. 281 et seq.; Sprecher (2020), p. 318.

[273] Nuffield Council on Bioethics (2018), par. 2.19.

[274] Hayashi et al. (2011).

[275] Cf. Hayashi et al. (2011, 2012).

[276] German Ethics Council (2019), p. 71; Cantz (2022), Chap. 2, Sect. 2.3 (this volume).

[277] German Ethics Council (2019), p. 71; with further detail Cantz (2022), Chap. 2, Sect. 2.3 (this volume).

[278] Advena-Regenry et al. (2018), p. 315.

5.4.3.2), the subsequent aspects concentrate on involving human iPSCs in this process.

Regarding the question, whether genome modifications on human iPSCs that are subsequently reprogrammed into gametes, qualify as prohibited interventions, one needs to take the following into account: According to a historical and teleological interpretation, the term "germ cell" as used in Art. 119 lit. a FedCst is to be understood in broad terms—not least by the legislator in the implementing legislation.[279] Since, from a medical point of view, iPSCs are the precursor cells of the artificial gametes, a genetic modification of the iPSCs in view of creating an artificial gamete would be included and prohibited by Art. 119 para. 2 lit. a FedCst. Subsequently, *de lege lata* it seems not permitted to modify iPSCs that are intended to be reprogrammed into germ cells. One may object that the genetic modification happens in the somatic cell,[280] *prior* to the reprograming and without the iPSCs functioning as a precursor cell. However, from the moment on, when genetically modified iPSCs are used to create gametes a violation of Art. 119 para. 2 lit. a FedCst seems taking place.[281] If no research privilege exists, researchers would be required to stop the research processes at such a point. Moreover, serious and professional research demands transparency as to the process and, hence, the further objective of modifying an iPSCs should be communicated at the beginning (Cf. Art. 17, cf. 16 HRA).[282]

5.4.3.4 Artificial Gametes

Especially in cases of infertile egg cells and sperm cells, in vitro created artificial gametes[283] promise new solutions for fertilisation. At the same time, they are suitable for germ line interventions as modifications can be conducted and controlled in the precursor cells, e.g. iPSCs or ESCs. They are highly interesting from a legal perspective as they have so far not been specifically regulated, instead they challenge the current legal norms. In order to analyse this complex topic, this contribution aims to establish a distinction between, firstly, the qualification of artificial gametes in law, secondly, the process of their creation and, thirdly, their use.

Art. 2 lit. e RMA concretises Art. 119 para. 2 sent. 1 FedCst. The constitution defines germ cells (simply) as being sperm cells and ova,[284] and is therefore not,

[279] Reusser and Schweizer (2014b), par. 23.

[280] Which is allowed according to Swiss law, as we saw above.

[281] Cf. Art. 18 para. 2 BMC, which is a bit less restrictive: "The creation of human embryos for research purposes is prohibited"; Radau (2006), pp. 213 et seqq; Boillet (2021), par. 32 and 42.

[282] In the same sense cf. ISSCR Guidelines (2021), para 3.3 Preclinical Studies: 3.3.4 Transparency and Publication (p. 32), and para 3.4 Clinical Studies: 3.4.3 Transparency and Reporting of Research Results (p. 37).

[283] Cantz (2022), Chap. 2, Sect. 2.3 (this volume).

[284] Federal Council's Dispatch RMA 1996, p. 247.

expressis verbis, restricted to naturally occurring in vivo germ cells.[285] In view of the fundamental right to a non-modified genome,[286] Art. 119 FedCst must be understood broadly. Taking into account the historic objective of the legislator, the purpose pursued by the norm,[287] and the contemporary Swiss and international framework, one can conclude that artificial, e.g. iPSC- or ESC-based, germ cells can be subsumed under the constitutional term "germ cells". Consequently, the norms dealing with human native germ cells are to be applied analogously to those created artificially and interferences with artificial gametes are covered by the prohibition. What means creation of artificial gametes? It is a "research that generates human gametes from any progenitor cell type in vitro, when this entails performing studies of fertilization that produce human zygotes and embryos. The gametes may be derived from human pluripotent stem cells, oogonia, or spermatogonial stem cells that have been maintained in vitro, and they may be genetically modified or not. Any human embryos obtained from such gametes must only be studied in vitro, or be used to derive stem cell lines, such as embryonic stem cells."[288]

Then the question is whether the creation of an artificial gamete already constitutes an "interference" according to the Constitution. As examined above, the prohibition in Art. 119 para. 2 lit. a FedCst also applies to precursor cells such as iPSCs and ESCs. During reprogramming and differentiation, the genome of iPSC-based germ cells is not artificially modified per se;[289] differentiation does not necessary require differentiation factors within the cell, only external factors are applied.[290] There is no artificial genetic modification of the base pairs, only haploidisation, i.e. halving of the genome during the natural process of meiosis.[291] Per se, the creation of genetically non-modified artificial gametes is not prohibited *de lege lata*.[292] However, according to the current status of research, reprogramming of somatic cells into iPSCs, for instance, might lead to a temporary or permanent modification of the cells.[293] As such, haploidisation of somatic cells in order to create gametes might provoke artificial alterations of the genome.[294] It is further probable that the current artificial gametes involve profound epigenetic

[285] This is by all means the case in German law as Advena-Regnery et al. (2018), p. 290; Advena-Regenry et al. (2018), p. 318, point out.

[286] Cf. Sect. 5.2.1.1.

[287] Cf. Federal Dispatch RMA, pp. 281 et seqq.; Art. 35 RMA, Art. 3 lit. b StRA, Art. 13 Biomedicine Convention.

[288] ISSCR Guidelines (2021), page: Culture of Human Embryos.

[289] However, as shown above (Sect. 5.4.3.1) using *genetically modified* human iPSCs as a basis for the creation of artificial gametes and thus modifying the human germ line is prohibited.

[290] Cf. Easley et al. (2012), p. 440.

[291] Advena-Regnery et al. (2018), p. 293.

[292] Likewise, Sprecher (2020), p. 288.

[293] Advena-Regenry et al. (2018), p. 318 with reference to Faltus (2016).

[294] Advena-Regenry et al. (2018), p. 318.

misregulations, leading to an impaired functionality of the gamete.[295] Therefore, this article assumes that the production of artificial gametes completely similar to natural ones is impossible. Hence, the production of artificial gametes due to "unintended" (epi)genetic modifications, as well as their subsequent "intended" genetic modifications, are currently prohibited.

As the legislator did not foresee iPSCs- or ESCs-based gametes,[296] specific regulation as to their usage is missing. The use of gametes artificially modified in their genome is limited in Art. 35 para. 2 RMA, which prohibits their usage for impregnation or in similar manners for the production of an embryo. Art. 119 para. 2 lit. c FedCst sets out important limitations on medically assisted reproduction: currently-known and future[297] procedures of medically assisted reproduction may only be used if infertility, or the risk of transmitting a serious illness, cannot otherwise be overcome. There are further restrictions on the use of techniques for medically assisted reproduction in order to conceive a child with specific characteristics or to further research. It is not clarified whether these reproductive techniques, i.e. methods of establishing a pregnancy without sexual intercourse, in particular, insemination, in vitro fertilisation with embryo transfer and gamete transfer (Art. 2 lit. a RMA), include techniques involving artificial gametes. Nevertheless, following the broad understanding of the term "germ cell" in lit. a of the article and the inclusion of future techniques, one can interpret this to mean that procedures using artificial gametes can be subsumed under the article. Subsequently, *de lege lata*, artificial gametes, assuming their genetic similarity to natural germ cells, may not be used for fertilisation as long as the constitutional requirements and those of the RMA are met (Art. 119 para. 2 lit. c FedCst, Art. 4 and 35 para. 2 RMA *e contrario*, Art. 5 RMA). Since the stipulated research limitation only refers to methods of establishing pregnancy,[298] other research objectives using artificial gametes are not prohibited. Hence, within the limits of Art. 119 para. 2 FedCst (e.g. para. 2 lit. b), using artificial gametes for research purposes is permitted under the current law. However, the question arises whether Switzerland does not need a more consistent regulation which, under Art. 119 FedCst, cover the development of artificial germ cells, artificial blastoids and artificial embryos for research purposes, including a strict regulatory framework for overseeing heritable genome editing.

Another relevant perspective is offered by scholars like Advena-Regnery, Enghofer and Sgodda who claim a continuous qualitative F and chronological intervention in the germ line through the application of artificial germ cells. Artificial germ cells, as such, did not receive the natural "signals" within the germ line and are derived from a long and artificial process of cell transformation, and no similar process is known in animals.[299] These arguments, together with the current

[295] Cantz (2022), Chap. 2, Sect. 2.3 (this volume).

[296] Cf. Sprecher (2020), p. 289.

[297] Reusser and Schweizer (2014b), par. 32; Art. 2 lit. a RMA.

[298] Seen above (Art. 2 lit. a RMA).

[299] Advena-Regnery et al. (2018), p. 286.

uncertainties surrounding the creation of artificial gametes and the discussion of the epigenetic risks of assisted procreation, should be considered when filling the existing legal loopholes.[300]

5.4.4 *Conditions and Limits of Germ Line Interventions and of Dealing with Embryos and Embryonic Stem Cells*

In summary, the following prohibitions and limitations relate to the topic of germ line interventions in Swiss law.

- Prohibition on intervening in the genome of germ cells and embryos (Art. 119 para. 2 lit. a FedCst, Art. 13 Biomedicine Convention, Art. 3 para. 1 lit. b, 24 StRA, Art. 35 para. 1 RMA; cf. Art. 25 HRA)[301]
  - Prohibition on using gametes which are artificially modified in their genome for impregnation or in similar manners for the production of an embryo (Art. 35 para. 2 RMA)
  - Excepted are cases in which the modification of germline cells is an unavoidable concomitant effect of chemotherapy, radiotherapy or another medical treatment that a person is undergoing (Art. 35 para. 3 RMA)
- Prohibition on creating an embryo for research purposes and on deriving stem cells from such an embryo ("therapeutic cloning") (Art. 119 para. 2 lit. a FedCst, Art. 18 para. 2 Biomedicine Convention, Art. 1 Additional Protocol Biomedicine Convention regarding Cloning, Art. 3 para. 1 lit. a, Art. 24 StRA, Art. 29 para. 1 RMA).
- Cloning (Art. 119 para. 2 lit. a FedCst; Additional Protocol to the Biomedicine Convention regarding Cloning)
  - Prohibition on creating a clone and deriving embryonic cells from a clone (Art. 3 para. 1 lit. c StRA)
  - Deriving embryonic cells from a clone or using such cells (Art. 3 para. 1 lit. d StRA)
- Prohibitions on dealing with surplus embryos
  - Using surplus embryos for any purpose other than the derivation of embryonic stem cells (Art. 3 para. 2 lit. a StRA)
  - Importing or exporting surplus embryos (Art. 3 para. 2 lit. b StRA)

[300] For an alluring contribution on the constitutional assessment of human iPSC-based gametes see Deuring (2019), pp. 350 et seqq.

[301] Note that these prohibitions do questionably not include human iPSCs; Art. 24 StRA seems further not prohibit the development of iPSCs into gametes.

  - Deriving stem cells from a surplus embryo after the 7th day of its development (Art. 3 para. 2 lit. c StRA)

- Prohibition on placing a surplus embryo used for stem cell derivation in a woman (Art. 3 para. 2 lit. d StRA)
- Prohibition of embryo donation and surrogated motherhood (Art. 119 para. 2 lit. d FedCst; Art. 4 RMA)
- Prohibition of ovum donation (Art. 4 RMA[302])
- Prohibition on introducing and fusing non-human germinal and genetic material into human germinal material[303]

  - Creating a chimera or a hybrid (Art. 3 para. 1 lit. c) or a parthenote (Art. 3 para. 1 lit. d StRA)
  - Deriving embryonic cells from a chimera, a hybrid or a parthenote and using such cells (Art. 3 para. 1 lit. d StRA)
  - **Please note**: The terms of (forbidden) chimeras and hybrids in the sense of the constitution and the RMA are narrower than the scientific terms. For example, the introduction of non-human genetic material into human somatic cells or the transplantation of human cells into a genetically modified mouse is not covered by the ban.[304]

- Prohibition of commercialisation of the human body or parts thereof (Art. 9 HRA)

  - Prohibition of trade in human germinal products or products derived from embryos (Art. 119 para. 2 lit. e FedCst.)
  - Note: the prohibition of trade does not apply to transplant products (Art. 7 para. 2 lit. b TA)
  - Importing or exporting an embryo of the types mentioned in Art. 3 StRA (Art. 3 para. 1 lit. e StRA)

- Prohibition on analysing, registering or making the genetic material of a person public without their consent (Art. 119 para. 2 lit. f FedCst; cf. Art. 27 revFADP, Art. 13 para. 1, 4 para. 5 FADP; Art. 16 et seq., 32–34 HRA; Art. 5 HGTA; with exception in Art. 27 HTGA; Art. 8, 57–60 Transplantation Act; Art. 321bis para. 1 Criminal Code; and already flowing in general from Art. 27 Civil Code)
- Prohibition on denying access to data relating to a person's ancestry (Art. 119 para. 2 lit. g FedCst; Art. 27 RMA)
- Duties to comply with the relevant international soft law, e.g. the ICH E6 Guideline for Good Clinical Practice (2021), and to take into account international research standards of private organisations, especially the ISSCR Guidelines (2021).

[302] Note that Art. 119 para. 2 FedCst does not cover ovum donation. Originally, it was thought to lift the ban stated in Art. 4 RMA in the revision in 2017.

[303] For more details see Wettlaufer (2018), pp. 337 et seqq.

[304] Reusser and Schweizer (2014b), par. 31; cf. Schweizer and Bernhard (2009).

5.4.5 Discussion

In conclusion, it must be stated that the current legal system contains an almost absolute ban on interventions in the genetic material of germ cells or embryos. *De lege lata*, following the wording of Art. 119 para. 2 lit. a FedCst, genetic interventions in germ lines are prohibited even if these are "closed", i.e. non-hereditary interventions (e.g. if the intervention is carried out in a germ line cell for research purposes, but the cell does not develop further and does actually not grow into a living being). According to the Swiss Federal Constitution—but not according to the Biomedicine Convention—it is irrelevant whether the intervention has a therapeutic purpose. Moreover, no distinction is made depending on whether or not cells are totipotent or pluripotent. The only exceptions to the prohibition are observational examinations and side effects during therapeutic treatments (cf. the limited analysis of genetic material of reproductive cells or embryos in vitro according to Art. 5a and Art. 22 para. 4 RMA). The broad legal framework also covers artificial gametes that have been reprogrammed from iPSCs. This contribution argues that the creation of artificial gametes is barred under the current law because of unintended genetic modifications during the process of creation. However, the analysis showed that different interpretations exist due to the lack of specific regulations. The importance and gravity of the topic make an interpretative solution inadequate and almost negligent. We urge the legislator, with reference to Art. 119 para. 2 1st introductory sentence FedCst, to clarify the legal requirements with respect to new techniques.

When amending these requirements, it would be necessary to either include the latest research status or to create broad norms applicable to any new technology (analogous to Art. 119 para. 2 lit. c FedCst). For example, the current definition of ESCs in Art. 2 lit. e StRA does not reflect state of the art research knowledge. Currently, the term only covers cells from in vitro fertilised embryos with the ability to differentiate into the various cell types, but not to develop into a human being, and the cell line derived therefrom. By applying CRISPR/Cas9 and subsequently transferring the nucleus into a decored germ cell, a fully-functioning entity could be generated. In contrast to Art. 2 lit. c StRA "embryonic stem cells", the definition of "germline cells" in the Art. 2 lit. f RMA contains more room for interpretation and thus covers new technologies more easily. Nevertheless, the entity or the cell type of the artificial gamete should be included[305] and should thus form the basis for further regulations. These could then provide concrete and appropriate legal certainty.[306]

At this point of time, the discussion about the extended possibilities offered by CRISPR/Cas9 in research on human cells is still in its beginning in Switzerland[307] and, despite repeated press reports, there are hardly any scientific articles or studies.

[305] I.e. because they open up new and prior unexpected possibilities of assisted reproduction, including selection procedures which are currently prohibited.

[306] Cf. Advena-Regnery et al. (2018).

[307] In contrast, the discussion on "green genetic engineering" is already very advanced, cf. e.g. Errass (2018).

The rapid scientific and technological developments, and especially the increasing precision of CRISPR/Cas9, will exacerbate the demand for gene therapy as a mean of treatment for serious hereditary diseases. Currently, there is a "lack [of] an adequate understanding of the fidelity and precision of techniques for genome editing of human embryos, as well as a full appreciation of the safety, ethics, and potential long-term risks and benefits to individuals born following such a process".[308] Sometime in the near future, the legislator will have to decide which procedures should be allowed and whether genetic engineered interventions in the germ line should be legitimised in the future—when health risks are excluded.[309] In cases of the most serious hereditary diseases, one will need to define to what extend the cure of such diseases may be restricted in light of the right to life and the right of personal integrity pursuant to Art. 10 FedCst.[310] However, in view of the existing safety risks and uncertainties of the technology, such as the possible formation of tumours when using IPSCs or of different epigenetic effects, germ line interventions with effects on born individuals are not yet justifiable.[311] For these reasons the ISSCR states that "basic and preclinical research is needed to minimize the potential harms resulting from intended and unintended edits, which could be passed to future generations, as well as direct or indirect effects of the editing process that could affect embryo viability or developmental potential. [...] It is important that the biological consequences of the intended genome edit are well understood, both for the immediate offspring and for future generations who might inherit it, in order to minimize the potential for an intended edit to have unintended deleterious consequences."[312] Swiss doctors, biologists, ethicists and lawyers should take part in the international discussion on a (temporary) moratorium[313] on the clinical application of germ line intervention. This is to be supported in view of the current risks and unknowable effects. Nevertheless, a possible step seems to introduce very specific exceptions for precisely limited research, for which the purposes of the research, e.g. developmental biology or human genetics, will most probably also need to be defined.[314] Where the current legal system also prohibits research on, for example,

[308] ISSCR Guidelines (2021), page: "Heritable Genome Editing". And idem: "This is described in more detail in the recent report, Heritable Human Genome Editing, from the International Commission on the Clinical Use of Human Genome Editing (National Academy of Medicine, National Academy of Sciences, and the Royal Society, 2020)".

[309] Sprecher (2017), pp. 1484 et seq.

[310] Analogously on the German regulation and with further remarks Taupitz and Deuring (2019), pp. 77 et seqq.; for an interesting discussion on eugenics see Rütsche (2010).

[311] Likewise, cf. Taupitz and Deuring (2019), p. 83.

[312] ISSCR Guidelines (2021), page: "Heritable Genome Editing". (for "consequences").

[313] Cf. Nationale Ethikkommission im Bereich der Humanmedizin (2016); cf. Advena-Regnery et al. (2018).

[314] One might think of an exemption similar to the amendment to the British Human Fertilisation and Embryology Act of 2008 (HFEA) and the Human Fertilisation and Embryology (Research Purposes) Regulations 2001. With a special licence an embryo can be kept and used for research purposes, but according to HFEA section (3) subsection (3) a licence cannot authorize "(a) keeping

artificial gametes and their genetic modification, freedom of research may allow such research to go ahead under strict guidelines. It is only through research that the existing safety risks can be investigated and minimised to the greatest extent possible. Permission for research would require an amendment to the constitution[315] and to the federal legal acts, but not a withdrawal from the Biomedicine Convention. The latter allows germ-line interventions, as described above, for therapeutic purposes as long as no modification of the genome of the offspring is conducted (Art. 13 Biomedicine Convention). Permitting research on artificially modified gametes, for instance, may be done for therapeutic grounds and does not necessarily have an effect on later generations, if the limits of preclinical and clinical trials are respected and a specialized scientific and ethical oversight process is established. Clear regulations, similar to the StRA, e.g. by an amendment to the StRA, would be necessary. As such, research would have to be restricted so that artificial fertilisation does never take place. This research privilege must, of course, not endanger human life from the time of nidation. In any case, a legal and ethical debate on the subject in the twenties of this century is indispensable.[316]

International cooperation in many research areas means that international, or at least European, regulations are needed today. Although in view of the various different national regulations, a meaningful global moratorium or norm set is unlikely, the signs of increasing international cooperation are to be welcomed. The *WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing,*[317] for example, is developing an international framework to govern the use of gene-editing technologies in people. As part of their work, the Committee favours a global register of studies that involve editing the human genome in order to increase transparency and to bridge the gap between the individual national frameworks, until a common one is found. According to Art. 18 StRA, the Federal Office of Public Health maintains at least a public registry of the embryonic stem cells from surplus embryos present in this country and of all swiss research projects on ESCs. Similarly, the efforts of the *International Commission on the Clinical Use of Human Germline Genome Editing* are to be assessed

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or using an embryo after the appearance of the primitive streak." Subsection (4) concretises for research: "For the purposes of subsection (3)(a) above, the primitive streak is to be taken to have appeared in an embryo not later than the end of the period of 14 days beginning with [the day on which the process of creating the embryo began], not counting any time during which the embryo is stored."

[315] Art. 119 para. 2 lit. a and c. Lit. c might require an amendment, as additional questions could be relevant (e.g. the age of the iPSCs donor).

[316] Speaking of the ethical debate, it seems worthy to note the difference between the different aspects of the discussions on genome editing in the extra-human and human sphere in Switzerland. Whereas in the extra-human area, the question of admissibility is rather a matter of positive law (cf. Art. 5 para 2 GTA, and the decision C-528/16 of the ECJ in 2018, defining genome editing on plants as gen-technology), here, ethical-legal considerations prevail (Cf. Taupitz and Deuring 2019, p. 76).

[317] For further information see https://www.who.int/groups/expert-advisory-committee-on-developing-global-standards-for-governance-and-oversight-of-human-genome-editing/about.

positively. The Commission is convened by the U.S. National Academy of Medicine, the U.S. National Academy of Sciences, the U.K.'s Royal Society and involves academies of sciences and medicine from around the world. It is in the process of developing a framework for scientists, clinicians, and regulatory authorities to be considered when assessing potential clinical applications of human germline genome editing, should society conclude that heritable human genome editing applications are acceptable.[318] In March 2020, the German Ethics Council, the British *Nuffield Council on Bioethics* and the French *Comité Consultatif National d'Éthique pour les sciences de la vie et de la santé* released a joint statement on the ethics of heritable human genome editing, demanding for clear joint actions regarding heritable human genome editing.[319] Finally, the ISSCR published in May 2021 the aforementioned new Guidelines for Stem Cell Research and Clinical Translation, the most precise and sophisticated rules for research and application.

5.5 Treatment of the Patient's Biological Data

Although Doctors have always dealt with information or data of their patients,[320] there is no doubt that digitalization in the healthcare sector is highly significant today. Especially biomedical research, be it on somatic human iPSCs or germ line interventions, is highly data driven. This leads to two confronting interests: on the one hand, the privacy interest of patients. This is due to the detailed and sensitive personal (genetic) data that is required for this eminently advantageous research.[321] On the other hand, the transparency of the data used in a research project is of great value for scientific discussions and subsequent researchers and serves to validate the findings.[322] For a long time, researchers were asked to make raw data generated by research projects available to researchers outside their own group (*data sharing).* Through the exchange of data, repetitive research can be avoided and the data may well be also used for drug and therapy development.[323] Data becomes particularly important in the field of personalised medicine, which includes diagnostic, preventive and therapeutic measures that are optimally tailored to an individual.[324] As such, personalised medicine should have a preventive effect, improve the quality of treatment and also enable statements to be made Fe on the future development of health.[325] One expects more effective therapies and fewer side effects from such

[318] The National Academies of Sciences, Engineering, and Medicine (n.d.).

[319] Comité Consultatif National d'Éthique pour les sciences de la vie et de la santé, German Ethics Council, Nuffield Council on Bioethics (2020).

[320] German Ethics Council (2019), p. 35.

[321] Cf. Pommering (2014), p. 60.

[322] Cf. Higher Education Funding Council for England et al. (2016).

[323] Schläpfer (2016), p. 137.

[324] Eckehardt et al. (2014), pp. 15 et seqq.; FOPH-working group "Personalised Medicine" (2017), p. 7.

[325] Cf. Uttinger (2015), par. 10.93.

tailor-made treatments.[326] However, to achieve these goals, information about the biological foundations of the human genetic data is required.[327] The central elements in this context are the analytical values of the person treated and, therefore, personalised medicine can only function in connection with research.[328] Additionally, it presupposes tracing of individual health data back to the specific person. This means that it is not possible to process anonymised data from which the identity of the person concerned cannot be inferred.[329] An important tool especially for personalised medicine is *big data,* which refers to a large volume of data from various sources and is characterised by its volume, variety and velocity.[330] In light of those conflicting interests, it is important to carefully regulate the usage of personal (genetic and biological) data, especially in connection with germline interventions.

In addition to these factors, current developments in Switzerland require an overview of the main factors that need to be met with regard to a patient's data: already in 2007, Switzerland approved the *eHealth Switzerland* strategy on the introduction of an electronic patient dossier in order to increase the quality of medical care and patient safety.[331] In line with the *eHealth Switzerland 2.0* strategy, the federal legislator introduced the Federal Act on the Electronic Patient Dossier of 19 June 2015 which entered into force in 2017 (EPDG[332]). It regulates the requirements for processing the data of the electronic patient dossier.[333] Hospitals must participate in the electronic patient dossier (EPD) and need to file the health information in the EPD, including medical secrets, from 2022 onwards.[334] Participation is voluntary for all other treatment providers such as general practitioners, pharmacies or Spitex services.[335] The EPD is also voluntary for citizens.

In this context, the various legal requirements on data protection have to be complied with. These are examined below.

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[326] Cf. Do Canto (2020), p. 178.

[327] Do Canto and Steiner (2019), p. 6.

[328] Pommering (2014), pp. 62 et seq.

[329] Uttinger (2015), par. 10.93.

[330] Eckehardt et al. (2014), pp. 141 et seqq; Schroeder de Castro Lopes and Schallnau (2019), p. 285; Cf. Sprecher (2018), pp. 497 et seq.; of interest is further Mathys (2015); Schweizer (2020b).

[331] Uttinger (2015), par. 10.47.

[332] German abbreviation; there is no English version available.

[333] Art. 1 para. 1 EPDG.

[334] The introduction of the national electronic patient dossier (EPD) was planned for April 2020, however, works on certifications have taken longer than expected. Currently (as of July 2020), it is becoming apparent that the certification procedures could be completed between autumn 2020 and spring 2021 (Konferenz der kantonalen Gesundheitsdiretorinnen und -direktoren 2020); for further information about the EPD see the website www.patientendossier.ch by e-healthsuisse, the coordination authority of the federal government and cantons, the Swiss Confederation and the conference of the cantonal health directors.

[335] "Spitex" is the abbreviation of hospital external help and care and is used in Switzerland to describe care at home. Spitex organisations provide services to people in need of every age group in order to support and enable life at home. For further information see https://www.spitex.ch.

5.5.1 Legal Framework

In Switzerland, the requirements of data protection vary according to the type of data in question. In line with international frameworks,[336] certain data, such as health data for example, is classified as being "sensitive", meaning that it is particularly worthy of protection and thus subject to stricter obligations. The term "health data" or "health-related data" describes data collected from various sources that can describe or influence a person's state of health. Included are, *inter alia*, information on people's health (e.g. symptoms), data from investigations (e.g. blood pressure, laboratory values) and results from genetic or other laboratory tests.[337] According to the revised Art. 6[338] of the revised European Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data of 1981 (European Convention for Data Protection, Convention 108), as well as to the last revision[339] of the Federal Act on Data Protection (see below), genetic data is also defined as sensitive data.[340]

In Switzerland, there is no single law explicitly regulating health data, but rather a combination of general and specific data protection laws. If certain rules are in conflict, the specific laws take precedence over the general protection law.[341] An overview of the applicable law is given below, before briefly highlighting current legislative developments (Table 5.2).

It is important to note that in private law the federal legislator regulates data protection binding only private hospitals.[342] In contrast, data protection in the public sectors is regulated by the federal government and by the Cantons (the states).[343] Since the public hospitals of the cantons and cities treat the great majority of patients,

[336] Especially the European Data Protection Convention 108 ("Convention 108") and its additional protocols.

[337] FOPH-working group "Personalised Medicine" (2017), p. 4.

[338] ***Art. 6 Convention 108 Special categories of data*** *"1. The processing of: (a) genetic data; (b) personal data relating to offences, criminal proceedings and convictions, and related security measures; (c) biometric data uniquely identifying a person; (d) personal data for the information they reveal relating to racial or ethnic origin, political opinions, trade-union membership, religious or other beliefs, health or sexual life, shall only be allowed where appropriate safeguards are enshrined in law, complementing those of this Convention. 2. Such safeguards shall guard against the risks that the processing of sensitive data may present for the interests, rights and fundamental free-doms of the data subject, notably a risk of discrimination*" (Letters (a)-(d) in sentence 1 added by the authors.).

[339] Finished on 25 September 2020.

[340] Differenzen Datenschutzgesetz, Stand 2 June 2020, Art. 4 lit. c No. 3; Uttinger (2015), par. 10.72; Mund (2005), p. 315.

[341] According to the common principle *lex specialis derogat legi generali*.

[342] However, according to the prevailing view of the cantonal data protection commissioners, cantonal data protection law is also applicable in private medical care institutions if they fulfill an assignment based on the cantonal list of hospitals (Cf. Rütsche (2012); according to a report written by the author).

[343] Cf. Brunner (2015), par. 10–12; Germany has similar regulations.

Table 5.2 Overview of the relevant regulations for Data Protection of Health Data [cf. Schroeder de Castro Lopes and Schallnau (2019), pp. 287 et seq.; Schweizer RJ (2020b)]

Regulation	Remarks
Art. 8 ECHR[a]	Human Right of Personal Data protection idem Art. 17 ICCR[b]
European Convention on Data Protection, ETS No. 108 (of 1981, amended 1999)	Important binding international framework for the protection of individuals with regard to automatic processing of personal data
Art. 13 para. 2 FedCst	The foundation of personal data protection in Switzerland, the fundamental right to protection against the misuse of personal data[c] This fundamental right is reinforced by Article 8 ECHR and Art. 17 ICCR
(Former) Federal Act on Data Protection (FADP) of 1992 resp. the revised FADP of 2020[d]	Sets out basic principles for the private sector and the sector of federal public authorities Defines health data as sensitive personal data to which specific requirements apply No comprehensive regulation of big data, but single and specific safeguards (Art. 11 revFADP, Art. 11a FADP; Art. 31 revFADP, Art. 17a FADP)
Data Protection Acts of the 26 Cantons (federal states)	Cantonal Data Protection Acts bind public cantonal hospitals and researchers (cf. below)
Swiss-US Privacy Shield[e]	Requires that the Federal Council, the legislature of the State concerned or the international body provides adequate data protection (Art. 13 para. 1 revFADP, Art. 6 para. 1 FADP) Section 14 deals specially with pharmaceutical and medical products
HRA and implementing ordinances	Concretises basic principles as to sectoral data protection law in the context of human research Defines the framework for processing health data, biological material and genetic data for scientific research purposes Export and storage of data (Art. 42–43 HRA) Includes data protection rules for enforcement organs
HGTA	Defines genetic data Prevents improper use of genetic data and their analysis Includes the right not to know (Art. 8 HGTA) Not applicable to genetic testing for research purposes
Transplantation Act[f]	Concretises basic principle Sets out the data protection framework for the stem cell register by the FOPH (cf. Art. 62)
RMA	Art. 6b refers to HGTA regarding the protection and communication of genetic data.

(continued)

Table 5.2 (continued)

Regulation	Remarks
Art. 321[bis] Swiss Criminal Code	Breach of confidentiality in research involving human beings is subject to criminal liability with limited exemptions (Art. 321[bis] para. 2)

[a] For more details: Reid (2019), for data access, collection and retention, as well as disclosure including health data see para. 73-009—para. 73-011; for aspects of reproductive medicine see para. 73-016; for health measures see para. 73-018; for physical and moral integrity see para. 73-021; Meyer-Ladewig and Nettesheim (2017)
[b] Schabas (2019), Art. 17 para. 25, 53 et seqq.
[c] In 2017 there was a parliamentary initiative to amend this constitutional article and introduce a right of self-determination with regard to information. However, this proposal was rejected at the time
[d] As a reaction to the European General Data Protection Regulation (GDPR) and the following change to the European Data Protection Convention, Switzerland, a member state to the Convention since 1998, revised the current FADP. On 25 September 2020, the Swiss Parliament adopted the total revision of the FADP. No group has the intention of holding the referendum. The Federal Council will decide when the revFADP will enter into force. On the basis of the current situation, it can be assumed that this will take place in Summer 2022. The revised FADP will be cited as "revFDAP" hereinafter
[e] For further instruments in relation to cross-border data transfers see https://www.edoeb.admin.ch/edoeb/en/home/data-protection/handel-und-wirtschaft/transborder-data-flows.html after the decision of the ECJ in the case C-311/18 of 16 July 2020, Data Protection Commissioner v. Facebook Ireland Ltd und Maximilian Schrems, in which the Court found the EU/US Privacy Shield inadequate. The ruling is not directly applicable to Switzerland, however, the Federal Data Protection and Information Commissioner will examine the judgement in detail and comment on it in due course (Federal Data Protection and Information Commissioner 2020)
[f] For detailed information of the data protection requirements in the Transplantation Act, see Mausbach (2009)

the handling of patient data at these hospitals is generally subject to cantonal data protection laws. As medical research is largely carried out at cantonal hospitals associated with cantonal universities, unless it is conducted by the pharmaceutical industry, medical research is also generally subject to cantonal data protection legislation. However, in the present context of research on human germ materials, ESCs, iPSCs, embryos, foetus, etc., it is largely special federal regulations which determine data protection in research and application (e.g. in reproductive medicine).[344]

5.5.2 Requirements for Data Protection

In general, processing, i.e. any operation with personal data irrespective of the means applied and the procedure in particular, collection, storage, use, revision, disclosure

[344] For further elaborations on data processing by cantonal organs see Waldmann and Oeschger (2011).

of personal data,[345] archiving or destruction of data, is unlawful (Art. 26 para. 1 in conjunction with Art. 4 lit. a, d revFADP). Specifically, it is forbidden to process the data in contravention of the principles set out in Art. 6 and 8 revFADP. However, processing can be justified, according to Art. 31 para. 1 revFADP, by consent from the data subject (cf. the conditions of a consent in Art. 5 para. 6 and 7 revFADP), by law (e.g. law enforcement), or in specific cases by an overriding private or public interest (e.g. research and statistics, provided that no individual data subject can be identified).[346] In cases where sensitive data such as health data (which, according to Art. 5 lit. c revFADP, includes genetic data) is concerned, more effective protection exists. The most relevant requirements for dealing with health data are examined below.

5.5.2.1 Basic Principles of Data Protection

In dealing with personal data, and even more so when sensitive data is involved, certain data protection principles need to be taken into account. The following principles[347] are mainly based on the Federal Act of Data Protection but may also be derived from the Convention on Data Protection 108 by the Council of Europe.

- **Principle of proportionality:** In line with the constitutional principle of proportionality (Art. 36 para. 3 FedCst),[348] which is also of mayor importance in international law,[349] the processing of personal data needs to be proportionate, i.e. the degree of data processing must not go beyond what is necessary (Art. 6 para. 2 revFADP, [Art. 4 para. 2 FADP]).
- **Principle of data minimisation:** The principle of proportionality also finds its expression in the principle of data minimisation, which implies that only such data should be processed as is actually required in order to achieve the purposes set for processing.[350] This means that health data, especially human genomic data[351] collection itself should be limited, promoting a responsibility *ex ante*. Depending on the case, this leads to anonymisation or pseudonymisation of the data (cf. Art. 6 para. 4 revFADP).

[345] Disclosing data includes making personal data accessible, for instance, by permitting access, transmission or publication (Art. 4 lit. d revFADP, [Art. 3 lit. f FADP]).

[346] Art. 16 et seq., 32–34 HRA; Art. 5 HGTA; Art. 8, 57–60 Transplantation Act; Art. 321bis para. 1 Criminal Code; and already resulting generally from Art. 27 Civil Code.

[347] Cf. Brunner (2015), par. 22.

[348] Cf. Hofstetter (2014).

[349] For further elaborations on proportionality in international law see Crawford (2011) and Gardam (2017).

[350] Schroeder de Castro Lopes and Schallnau (2019), p. 284.

[351] Cf. Art. 5 revFADP, Art. 4 FADP.

- **Purpose limitation principle:** related to the idea of data minimisation, is the purpose limitation principle which stipulates that personal data may only be used in the cases indicated at the time of collection. The principle is based on Art. 5 para. 3 revFADP (Art. 4 para. 3 FADP) but can also be found in the Transplantation Act (Art. 59 para. 5), the new HGTA (Art. 9) and in the modernised European Data Protection Convention (Art. 5 para. 4 let. b).
- **Requirement of accuracy:** Anybody who is processing personal data is obliged to ensure the accuracy of such data in accordance with Art. 5 para. 6 revFADP (Art. 5 FADP). Any person is allowed to demand that inaccurate personal data be corrected (Art. 32 revFADP).[352]
- **Data security:** Personal data needs to be secured against unlawful use, i.e. external threats (e.g. hackers) and internal threats (e.g. poorly trained employees) through appropriate technical and organisational measures (Art. 8 revFADP, [Art. 7 FADP])
- **Principle of transparency:** According to Art. 6 para. 3 revFADP (Art. 4 para. 4 FADP) and the principle of good faith in the collection of personal data, particularly the purpose of its processing must be evident to the data subject (cf. Art. 19 revFADP, [Art. 14 FADP]). The right ranges from procurement to storage. The data controller[353] is required to inform the data subject about the collection of personal data; this obligation to inform also applies if the data is not collected from the data subject itself but from any other source (Art. 19 para. 1 clause 2 revFADP, Art. 18a FADP).
- **Principle of access:** According to the principle of access, every person always has the right to obtain, free of charge, information from the data controller as to whether personal data relating to him/her is being processed. This right is part of the fundamental right of Art. 13 para. 2 FedCst and Art. 8 ECHR and it is protected in case of breach by criminal punishment according to Art. 60 revFADP.[354] The data subject shall be provided with the information necessary to enable him/her to exercise his/her rights under this Act and to ensure transparent data processing (Art. 25 et seqq. revFADP, Art. 8 et seqq. FADP). The data controller is obliged to provide indications about the data location and usage (cf. Art. 25 para. 2 revFADP, [Art. 4

[352] FSCt 1C_597/2020, cons. 6.3; ECtHR, Catt v. The United Kingdom, 43514/15 [2019], para. 127).

[353] The "data controller" is any private person or federal body that decides on the purpose and content of a data file (Art. 3 lit. i FADP). In the drafted revFADP, the term describes the private person or federal body who, alone or together with others, decides on the purpose and the means of the processing (Art. 4 lit. i revFADP). The data protection legislation of the Cantons is using the term "person responsible" or "data controller".

[354] ECtHR, Roche v. United Kingdom, 32555/96 [2005], para. 157-168; Joanna Szulc v. Poland, 43932/08 [2012], para. 93; Segerstedt-Wiberg and others v. Sweden, 62332/00 [2006], para. 99; BGE 122 I 153 cons. 6b/aa, 162; 127 V 219 cons. 1a/aa, 222; 138 I cons. 4.1, 23, ns cons. 7.5.2, 38; 144 II 126 cons. 8.3.7, 153.

para. 4 FADP]). In this context it is important that Art. 119 para. 2 lit. g FedCst, corresponding with Art. 7 para. 2 CRC, stipulates the following fundamental right, with horizontal effect: "Every person shall have access to data relating to their ancestry".[355]

- **Lawful processing and processing in good faith**: According to Art. 4 para. 1 and 2 FADP, data may only be processed lawfully. Thus, public sector organs are bound to a legal basis (Art. 34 revFADP, [Art. 17 FADP]) and the Swiss Constitution already adopted the principle of good faith (Art. 5 para. 3 FedCst). As seen above, Art. 31 revFADP (Art. 13 FADP) covers specific justifications for data processing. The new FADP provides for a right to advice. If the data protection impact assessment (Art. 22 revFADP) shows that the planned processing entails a high risk to the personality or fundamental rights of the data subject, the data controller shall seek the opinion of the Commissioner[356] in advance before taking the measures envisaged by himself (cf. Art. 21 revFADP).
- **Research privilege:** Art. 31 para. 2 lit. e[357] and Art. 39 revFADP (Art. 13 para. 2 lit. e FADP) provides a list of circumstances in which the overriding interest of the person processing the data is particularly taken into account. For instance, this is the case when personal data is processed for purposes not related to a specific person, in particular for the purposes of research, planning and statistics, and if the results are published in such a manner that the data subjects cannot be identified.

[355] Boillet (2021), par. 58 et seqq.; Belser and Molinari (2015c), par. 46 et seq.; both authors criticise the restrictive regulation in Art. 24 and 27 MPA. Concerning Art. 7 CRC see Schmahl (2021), Art. 7 par. 16 et seqq.; ECtHR, Gaskin v. United Kingdom, 10454/83 [1989], para. 89.

[356] In Switzerland, the Federal Data Protection and Information Commissioner (Commissioner) supervises the application of federal data protection legislation. He supervises federal bodies as well as private bodies, assists federal and cantonal authorities in the field of data protection and gives his opinion on draft Confederation legislation. Further, he cooperates with data protection authorities in the Cantons and abroad in other states. He informs the public about his findings and recommendations. Additionally, he maintains and publishes the Register for Data Files. For more information about the the Commissioner see Art. 43-59 revFADP, and cocerning the crossborder disclosere of personal data see Art. 16 and 17 revFADP.

[357] Art. 31 para. 2 lit. e revFADP: "e. The controller processes personal data for purposes not relating to a specific person, in particular for the purposes of research, planning and statistics, provided that the following requirements are fulfilled:

1. The controller shall anonymize the data as soon as the purpose of the processing allows for it or shall take reasonable measures to prevent the identification of the data subjects if anonymization is impossible or requires a disproportionate effort.
2. Sensitive personal data is disclosed to third parties in such a manner that the data subjects may not be identified. If this is not possible, measures must be taken to ensure that third parties only process the data for non-personal related purposes.
3. Results are published in such a manner that the data subjects may not be identified."

5.5.2.2 Selected Principles of Data Protection

5.5.2.2.1 Voluntary and Informed Consent

As stated above (cf. Sect. 5.3.1), every treatment with data must be consented. In line with this principle of informed consent, the data subject is to be informed appropriately about the collection of personal data (Art. 19 revFADP). According to Art. 19 para. 1, such duty of information also applies when data is not collected from the data subject.[358] In this case, the data subject has to be informed, apart from the information on the controller's identity, the purpose of processing and the recipients to which personal data is disclosed, especially on the categories of data collected.[359]

The consent to the use of data is to be given specifically and voluntarily. In the case of sensitive data,[360] it must be given expressly (this rule applies in addition to Art. 16 et seq. HRA, Art. 5 et seqq. HGTA, Art. 6 para. 7 lit. a revFADP, Art. 4 para. 5 FADP). According to the new FADP this explicit consent is also required for cases of *profiling* by a private person (in case high risk) or a federal authority (Art. 6 para. 7 lit. b, c revFADP).[361] Thereby, *profiling* means any automated processing of personal data consisting in using such data to evaluate certain personal aspects relating to a natural person, in particular to analyse or predict aspects relating to that natural person's performance at work, economic situation, health, personal preferences, interests, reliability, conduct, whereabouts or movements (Art. 5 lit. f. revFADP). Such a *profiling* is of high risk, if it leads to a linkage of data, which permits an evaluation of substantial aspects of the personality of a natural person (Art. 5 lit. g. revFADP). In the health care area, a medical report (e.g. for the disability insurance) of chronically painful people as well as medical reports of mentally ill people (e.g. endogenously induced or trauma-induced) can, indeed must, be considered a high-risk profiling. In order to comply with the requirement of an explicit consent, it should generally be given in written form.[362] And should be documented. The consent is further to be kept *à-jour* and should be immediately modified and supplemented in case of new data processing (remember, that the consent may be revoked at any time).

[358] The natural person whose personal data is processed (Art. 5 lit. b revFADP).

[359] Art. 19 para. 3 revFADP.

[360] Cf. Art. 5 lit. c revFADP; including genetic data (Art. 5 lit. c. para. 3 revFADP).

[361] At present, the additional requirements of Art. 6 para. 7 revFADP regarding explicit informational consent do not apply in cantonal and communal hospitals and nursing homes and other cantonal health care facilities, unless a canton follows the concept of the federal legislature. At best, one could argue that a graduated form of consent corresponds to a general legal principle of Swiss data protection law.

[362] Federal Council's Dispatch HRA, p. 8106; Art. 16 para. 1 HRA.

5.5.2.2.2 Secondary Use of Sampled Biological Data

Of particular relevance are the norms regulating the secondary, or further, use of sampled biological data. The "further use" requires the data to be already available beforehand, i.e. that it has been extracted—with the required consent (cf. Sect. 5.3.1)—for a reason other than for research (e.g. during a patient's treatment).[363] This further use is broadly understood and includes, *inter alia*, the collection of the sampled data, its storage, disclosure and transfer (cf. Art. 24 HRO). According to the principle of purpose limitation (Art. 5 para. 3 revFADP, Art. 4 para. 3 FADP), a change in the purpose of the collected data requires a legal reason or approval by the respective individual.[364] It is relevant to distinguish these changes of the research purpose from Art. 17 HRA, which covers the consent given for further use directly at the time of the first data collection.[365]

The requirements for such further use are regulated by Art. 32–35 of the HRA and Art. 24–32 of the Human Research Ordinance (HRO). Thus, modified models of consent are introduced according to a *risk-based approach.*[366] As such, different consent requirements exist depending on (1) the kind of health-related data used, (2) the type and manner of further use, and (3) the "openness" of the purpose of use.[367] Regarding the first aspect, the HRA differentiates between, firstly, biological material and genetic data (covered in Art. 32 HRA) and, secondly, non-biological material and non-genetic data (covered in Art. 33 HRA). Genetic data is defined as being information derived from people's genes and obtained by genetic testing (Art. 3 lit. g HRA, genetic testing is defined in Art. 3 lit. a HGTA). Biological material in the sense of Art. 3 lit. e HRA encompasses organs, tissue and cells (including germ cells) and body liquids such as blood or urine.[368] According to the Federal Council, the information content of non-biological material or non-genetic health-related data is manageable and thus lower hurdles need to be taken into account.[369]

As to the second aspect, all kinds of data can be characterised according to the type and manner of further data use. In this regard, data used is separated into (a) un-coded (or identifiable)[370] data, (b) coded (or pseudonymised/reversibly-

[363] Rudin (2015b), par. 4.

[364] Cf. Schläpfer (2016), p. 140.

[365] Rudin (2015b), par. 5.

[366] Cf. Art. 118*b*, para. 1 FedCst "The Confederation shall legislate on research on human beings *where this is required in order to protect their dignity and privacy*. [. . .]" (highlighting added); Federal Council's Dispatch HRA; Rütsche and D'Amico (2015), par. 21 et seqq.; Van Spyk (2015), par. 28 et seqq.

[367] Cf. Rudin (2015b), par. 15–19; cf. Schroeder de Castro Lopes and Schallnau (2019), p. 289.

[368] Federal Council's Dispatch HRA, p. 8095.

[369] Cf. Federal Council's Dispatch HRA, pp. 8083, 8121.

[370] As Rudin (2015b), N 11 highlights, the terms used in the HRA are misleading. This is why Rudin introduces further descriptions which are given in parentheses in this text.

Table 5.3 Consent requirements for further usage of biological material and genetic or non-genetic health-related data [cf. Rudin (2015b), p. 14, translated from German into English and slightly adjusted; cf. Schroeder de Castro Lopes and Schallnau (2019), p. 291.]

Manner of further use	Biological material and genetic data (Art. 32 HRA)	Non-genetic health-related data (Art. 33 HRA)
Un-coded (identifiable)	For a specific research project with informed consent	For research purposes in general with informed consent (general consensus)
Coded (pseudonymised/ reversibly anonymised)	For research purposes in general with informed consent (general consensus)	For research purposes in general with prior information and without the use of the right to opt out
Anonymised (irreversibly anonymised)	For research purposes in general with prior information and without using the "right to opt out"	Beyond the scope of the FADP/ HRA and allowed

anonymised) data, (c) anonymised (or irreversibly anonymised) data.[371] As to the third aspect, the consent requirement differs according to whether the data is to be used for a specific research project or in a general manner (e.g. because the research project is not known at the time the consent is requested). The rules regarding further use can be summarised in accordance with Rudin as follows (Table 5.3).

By way of a general agreement, which is required for pseudonymised biological material and genetic-data, as well as in cases of un-coded health-related data, people accept that their data and material might be used for—at the time of the consent—non-defined future research-projects.[372] Thus, a kind of blank authority is issued,[373] which does not limit the data usage.[374] According to Art. 29 para. 1 HRO, the information provided to individuals must be either written or oral, however, for the general agreement the written format is required (Art. 29 para. 2 HRO, exceptions according to Art. 9 HRO).

If the biological material or the genetic data has not been anonymised from the beginning (e.g. in the context of treatment), and was subsequently anonymised for research purposes in general,[375] the consent of the affected person is required in the

[371] Rudin (2015b), par. 9 et seqq.; In light of the rapid technological development and eventual future possibilities to de-anonymise data, the current ruling in the HRA seems questionable. For similar thoughts see Sprecher (2018), pp. 532 et seqq.

[372] Sprecher (2018), p. 527.

[373] In 2017, the Swiss Academy of Medical Science and the Swiss Ethics Committees for Human Research published a legally-non-binding proposal regarding the general agreement. The proposal was broadly discussed, developed and unified in 2018 and is available via the following link https://www.unimedsuisse.ch/de/projekte/generalkonsent. The template is complemented by the work of the Swiss Biobanking Platform, as well as by the Swiss Personalized Health Network (see Sprecher 2018, p. 528).

[374] Baeriswyl (2015), par. 74.

[375] Rudin (2015a), par. 23; the HRA is not applicable to research with anonymised biological material and health-related data that was collected in anonymised form (Art. 2 para. 2 lit. b, c HRA).

form of "not-using the right to opt-out". The person concerned must be informed in written or oral form (Art. 30 HRO) and must not have subsequently dissented. According to Art. 32 para. 3 sent. 2 HRA, the rules regarding the right to opt out follow Art. 22–23 HRA. This opt-out solution bears the questionable risk of nudging a person towards a higher level of consent.[376] One may further question the ability of the patient to fully comprehend the results of his/her general agreement or of not opting out.[377] Therefore, and in light of possible future techniques to de-anonymise this data, it seems generally questionable whether the exceptions on informed consent in the research sector are compatible with the clear requirements in Art. 118*b* FedCst.[378]

5.5.2.2.3 Rules Concerning the Storage, Archiving and Destruction of Health and Genetic Data

Another relevant aspect in relation to dealing with data protection is data storage and preservation. Genetic Data may only be stored, e.g. in files of the research institutes or in the electronic patient dossier (EPD), as long as necessary for treatment, for secondary use, or according to cantonal requirements (Art. 11 new HGTA). According to Art. 43 HRA anyone storing health-related personal data for research purposes is required to take appropriate technical and organisational measures to protect such data. Art. 18 ClinO specifies the appropriate measures and i.a. obliges the storing party to prevent unauthorised or accidental disclosure, modification, deletion or copying of health-related personal data. If biological materials such as tissue, blood, DNA or proteins from research projects which are linked to donor data, particularly clinical and epidemiological data, is organised collectively in great numbers, one refers to biobanks.[379] For instance, apart from direct extraction, iPSCs can be processed from frozen cell preparations stored in biobanks.[380] Biobanks are particularly important in connection with personalised medicine, as the latter relies on this linkage between the enormous amount of genomic data, and individual health data and other personal data.[381] Because of this valuable linkage, the risks for the patient's data protection increases. For example, reference data is not constantly irreversibly anonymised so that it can be continually updated.[382] Instead, it is at most encrypted, i.e. pseudonymised with one or more keys (codes).[383] Besides these relevant aspects, there is no specific regulation applicable to biobanks despite

[376] Rudin (2015a), par. 26.

[377] E.g. Aebi-Müller (2020), p. 6; Sprecher (2018), p. 532.

[378] Equally critical Belser and Molinari (2015b), par. 33–37.

[379] Nationale Ethikkommission im Bereich der Humanmedizin (2015), par. 2.

[380] Cantz (2022), Chap. 2, Sects. 2.2 and 2.3 (this volume).

[381] Nationale Ethikkommission im Bereich der Humanmedizin (2015), par. 5.

[382] Art. 31 para. 2 lit. e revFADP is indefinite in this regard.

[383] Nationale Ethikkommission im Bereich der Humanmedizin (2015), par. 28.

several demands for a law regulating this area since 2015.[384] Therefore, currently, the only regulation are the norms regarding retention in the HRA; there is no specific regulation or law applicable to biobanks as yet.

The question also arises how long patient data, or the data of research participants, needs to be stored after the treatment or project has ended. The federal data protection law does not provide for any specific retention periods and, therefore, pursuant to the principle of proportionality, data which is no longer required must be destroyed. As a rule of thumb, a general limitation of 10 years storage[385] is often applied in practice, but cases may differ and in some cantons the cantonal health law provides for precise retention periods.[386] In the canton of Zurich, for instance, the Patients Act stipulates that the patient's file must be kept for 10 years after the last treatment. If it is in the interest of the patient or of research, the hospital may keep the files for 30 years and, in consultation with the relevant archives, for 50 years (Art. 17 et seqq. Patients Act Zurich). In the canton of Berne, treatment documents are to be kept for as long as they are of interest to the patient's health, but for a minimum of 10 years after the end of the treatment. Records of treatment of children and adolescents up to the age of 18 and on the birth process must be stored for at least 20 years. Moreover, for treatments whose risks may, in the normal course of events, only materialise at a late stage, an appropriately longer retention period must be provided for (e.g. Art. 6 Patient Rights Ordinance Berne).[387] With regard to laboratory genetic tests, documents which are created based on quality management systems and external quality control need to be kept for 5 years and test reports must be kept for 30 years based on the federal Ordinance on Human Genetic Testing.[388] For the transplantation of human organs, tissues and cells, including transplant products such as iPSCs, the Transplantation Act stipulates the documentation of all relevant events. The documentation must be kept in such a way that the data can be traced back to the patient (Art. 34 lit. a Transplantation Act). The retention period is 20 years for all important documents (Art. 35 para. 1 Transplantation Act).

[384] Nationale Ethikkommission im Bereich der Humanmedizin (2015); critically Do Canto (2020), p. 180; Sprecher (2017); Motion Ruiz; Interpellation Michaud Gigon.

[385] Art. 26 para. 2 Health Law Berne in conjunction with Art. 6 para. 1 Patients Right Ordinance Canton Berne; § 18 para. 1 Patient Act Zurich; § 16 para. 1 Ordinances to the hospital law Canton of Basel City, Art. 57 Loi de la santé Canton of Genf; Art. 87 Abs. 5 Loi sur la santé publique Canton Vaud.

[386] Eidgenössischer Datenschutz- und Öffentlichkeitsbeauftragter (n.d.).

[387] Importantly, the Code of Obligations was revised in 2018 and by January 2020 the revised Art. 128a was introduced which stipulates that claims for damages or satisfaction arising from an injury or death in breach of contract are prescribed in absolute terms after 20 years. One can expect relevant changes in the cantonal health laws.

[388] There is no English version available, the German title is "Verordnung über genetische Untersuchungen beim Menschen". It is to be expected that the ordinance will be adapted to the revised HGTA (cf. Art. 28 et seqq., 30, 31 et seqq., 34 et seqq.).

5.5.2.2.4 The Right Not to Know

Resulting from the contractual relationship between patient and doctor, as well as from the principle of self-determination in Art. 10 para. 2 and Art. 13 para. 2 FedCst, every person has a general right to information (Art. 25 et seqq. revFADP, Art. 7 new HGTA), as well as, more specifically, the right to learn about the research results of genetic testing.[389] As a counterpart, the right to deny access to information on the genetic material exists:[390] according to Art. 8 new HGTA, every person[391] has the right to refuse to receive information about his or her genetic status, without giving any justification.[392] In order to be able to decide about the Right (Not) To Know, a comprehensive consultation with the doctor is required (cf. Art. 20–24 new HGTA). Also excluded from the Right Not To Know the genetic data, are those cases in which the genetic examination was ordered by a court or an authority, e.g. for identification purposes (Art. 49–51 new HGTA).[393] The right not to know is repeated in the field of human research: for instance, Art. 8 para. 1 HRA stipulates that the person concerned may waive the right to know results concerning his or her health.[394]

5.5.3 Discussion

As shown above, current data protection is not regulated by one specific law, rather a multitude of federal and cantonal acts (cf. FedCst, FADP, HRA, StRA, HGTA, RMA) apply in the field. Thus, it is important to note that, despite their fragmentation, the conjunction of these acts—like in the field of germ line interventions—provides a tight framework and important principles when dealing with health data. Through the revision of the HGTA, these fragmented laws are at least increasingly interlinked as principles, such as the right not to know (Art. 8 HGTA), are now also applied in related laws. Interestingly, when dealing with health data the classical concepts of data protection, e.g. the private law justification of informed consent or e.g. in public law the need for a legal basis, do not apply in parallel. On the contrary, specific very limited processing rights with strict requirements concerning information, advice and consent do exist. The HRA, in particular, contains extensive information requirements for research, as well as for medical treatments and

[389] Federal Council's Dispatch HGTA 2002, p. 7398.

[390] Federal Council's Dispatch HGTA 2017, p. 5666.

[391] Not only the person examined, but everybody (e.g. in the case of diseases which are transferred to the offspring). This is especially valuable for blood relatives; Cf. Rieder (2016).

[392] Errass (2021), Chapter 3, § 7 V.

[393] Cf. Büchler and Michel (2014), pp. 303 et seq.; on the right not to know in the context of genetic examinations, including the different positions in literature as to the question whether the patient needs to be informed of his or her right not to know after the genetic examination and prior to communication of the results, see Hollenstein (2014).

[394] A reservation to the right not to know seems appropriate for medical applications, i.e. when the doctor has a duty to act.

interventions in the genome—whether in iPSCs in regenerative medicine (e.g. treatment of macular problems) or in germ line interventions to overcome (one day) monogenetic hereditary diseases. In addition, there are general indirect access restrictions, for example, in Art. 5 and 5a RMA. It is further interesting how the upcoming version of the HGTA regulates surplus data (cf. Art. 3 lit. n, Art. 9, Art. 27 new HGTA), as this was so far only found in criminal law with regard to tapped data.[395]

Although several relevant frameworks apply, the short elaboration above shows that certain aspects of data protection may require further evaluation. In relation to data storage and preservation, the lack of adequate regulation of biobanks is unsatisfactory. Despite the cantonal health or patient laws often providing data preservation periods, not all cantons regulate the topic in the same detail and demand sufficiently long storage periods for genetic data. Moreover, private research groups are not bound by cantonal norms. As a consequence, storage periods might be too short in certain fields.

5.6 Conclusion

The aim of this contribution was first to present the Swiss legal framework applicable to research on human iPSCs. After this overview, the requirements for combined gene/cell therapies using genome edited iPSCs differentiating into somatic cells were examined. Section 5.4 of this report dealt with the topic of germ line intervention which can be conducted either on embryos or on germ cells, using as a source iPSCs or ESCs. Germ line interventions will become increasingly relevant due to further developments of gene editing methods, such as CRISPR/Cas9. In particular, the interventions on embryos, germ cells and stem cells, and thus genome edited iPSCs differentiating into gametes, were considered. Subsequently, the relevant norms regarding the protection of genetic data were examined.

With regard to the regulatory landscape of Switzerland for iPSCs, the picture is one of a historically grown patchwork: there is neither a health constitution in the strict sense, nor any directly applicable legislation on somatic gene/cell therapies. At the same time, various constitutional provisions, especially Art. 118*b*, 119 and 119*a* FedCst—which is actually extraordinary in international comparison—and various implementing laws are applied selectively. The TPA regulates the approval of drugs and is also applicable to transplant products, including iPSCs, the HRA sets out general regulations for clinical research and data protection, and the Transplantation Act focuses mainly on transplantations. The RMA regulates reproductive medicine and, although there is a law on stem cell research, the StRA, only embryonic stem cells are covered so far. The HGTA will cover almost all studies of the human

[395] On the limited use of random finds in the secret surveillance of private communications in criminal proceedings: cf. Art. 272 para. 2 Swiss Code of Criminal Procedure, BGE 144 IV 254, E. 1.3, 157.

genome but excludes studies that are covered by previous special laws.[396] Although the standards contained in these laws already set numerous limits and requirements for the handling of iPSCs and genome editing, it is becoming apparent that the existing regulations are partly lagging behind the technical developments. In some legal frameworks, certain definitions are inadequate (cf. gametes), a number of regulative requirements will soon no longer seem appropriate (cf. a transplantation of iPSC-based gametes would only require a notification to the responsible authority) and there is too much room for legal interpretation in highly relevant areas. Not much has really changed in Switzerland since about 2000 in the field of genome editing—with the exception of developments concerning PGD and PSG and the revision of the HGTA. On the positive side, the constitutional principles protect fundamental values and are rarely contested. In addition, the NEK and TA-Suisse, with their reports on genome editing, are supporting a public debate on the topic. Further examinations of the topic and all its facets are desirable.

In view of the situation *de lege lata* just described, the thoughts developed on the situation *de lege ferenda* will be summarised. First and foremost, there seems to be a need to discuss the topics mentioned in order to raise awareness as to the current legal situation and the scientific status quo. This should be done by way of a multi-stakeholder approach involving scientists, ethicists, politicians and the general public. In addition, it is important to update the current legal framework according to the status quo in research, e.g. broaden the definition of germ cells in the StRA and possibly adopt legislation regarding the development and use of iPSCs and the fields of human genome editing. Given the insufficient knowledge about the long-term (side) effects and risks posed by gene therapy using genome editing,[397] the need for further examination and discussions through international cooperation seems all the greater. Furthermore, genetic methods have so far been too immature to allow germline interventions in humans with the help of genome editing.[398] Before genome editing interventions in humans can be approved, the consequences must be completely clarified. Without touching upon the fundamental values of the Swiss constitution, this contribution aims to promote the discussion on a research privilege for artificial gametes based on iPSCs and on further possibilities of genome editing methods. Provided there are rigid limits, a research privilege would allow scientific findings to be obtained, which would in turn form the basis of an ethical-legal discussion. One could imagine a specific research legislation or an amendment of the StRA to regulate the details of such an approach, including specific privacy protection rules. As a matter of course, in view of the cross-border reality of scientific research, international cooperation is the basis of any development (cf. Sect. 5.4.5). Thus, existing international efforts, e.g. to promote international research principles, should be supported to the greatest extent possible and an accession to international forums would be constructive.

[396] Cf. Sprecher (2020), p. 323.

[397] Cf. Cantz (2022), Chap. 2, Sect. 2.4 (this volume); cf. Lang et al. (2019), p. 148.

[398] ISSCR Guidelines (2021), page: "Heritable Genome Editing"; Lang et al. (2019), p. 177.

Legal Acts

Additional Protocol Biomedicine Convention on Biomedical Research	CETS No. 195; Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research of 25 January 2005; https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/195
Additional Protocol Biomedicine Convention on Cloning	CETS No. 168; Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings of 11 January 1998; https://rm.coe.int/168007f2ca
Additional Protocol Biomedicine Convention on Transplantation	CETS No. 186; Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin of 24 January 2002 (ratified by Switzerland on 10 November 2009); https://rm.coe.int/1680081562
AO EPÜ 2000	SR 0.232.142.21; Ausführungsordnung zum Europäischen Patentübereinkommen (AO EPÜ 2000), Angenommen vom Verwaltungsrat am 7. Dezember 2006, in Kraft getreten für die Schweiz am 13. Dezember 2007, no English version; https://www.admin.ch/opc/de/classified-compilation/20072183/index.html#
Charter of Fundamental Rights of the European Union	2000/C 364/01; Charter of Fundamental Rights of the European Union; https://www.europarl.europa.eu/charter/pdf/text_en.pdf
Clinical Trial Ordinance (ClinO)	SR 810.305; Verordnung über klinische Versuche in der Humanforschung (Verordnung über klinische Versuche; KlinV) vom 20. September 2013; Ordinance on Clinical Trials in Human Research (Clinical Trials Ordinance, ClinO) of 20 September 2013; https://www.admin.ch/opc/en/classified-compilation/20121176/index.html
EU-Directive 1998	98/44/EC; Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998on the legal protection of biotechnological inventions, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31998L0044&from=EN
European Convention for Data Protection, Convention 108	CETS No. 108; European Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data of 198; https://www.coe.int/en/web/data-protection/convention108-and-protocol
European Convention of Human Rights (ECHR)	European Convention of Human Rights of 4 November 1950; https://www.echr.coe.int/Documents/Convention_ENG.pdf

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European Patent Convention	SR 0.232.142.2; Convention on the Grant of European Patents of 5 October 1973; https://www.epo.org/law-practice/legal-texts/html/epc/2016/e/ma1.html
European Regulation (EC) No. 1394/2007	(EC) No 1394/2007; Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004; https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF
Federal Act on Data Protection (FADP) of 1992	SR 235.1; Bundesgesetz über den Datenschutz (DSG) vom 19. Juni 1992; Federal Act on Data Protection (FADP) of 19 June 1992; https://www.admin.ch/opc/en/classified-compilation/19920153/index.html; The final text of the parliamentary discussion on the revision of the Federal Data Protection Act (revFADP) is available via https://www.admin.ch/opc/de/federal-gazette/2020/7639.pdf, the consultation period ends on 14 January 2021; BBl 220 7639
Federal Act on the Electronic Patient Dossier	SR 816.1; Bundesgesetz über das elektronische Patientendossier (EPDG) vom 19. Juni 2015; no English version; https://www.admin.ch/opc/de/classified-compilation/20111795/index.html
Former Swiss Federal Constitution (fFedCst)	SR 101; Bundesverfassung der Schweizerischen Eidgenossenschaft vom 29. Mai 1874; no English version; no online version
Gene Technology Act (GTA)	SR 814.91; Bundesgesetz über die Gentechnik im Ausserhumanbereich (Gentechnikgesetz, GTG) vom 21. März 2003; Federal Act on Non-Human Gene Technology (Gene Technology Act, GTA) 21 March 2003; https://www.admin.ch/opc/de/classified-compilation/19996136/index.html
GMP Directive	Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use; https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003L0094&qid=1648149876388&from=EN
Helsinki Declaration	World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subject; https://www.who.int/bulletin/archives/79(4)373.pdf
Human Fertilisation and Embryology Act (HFEA)	1990 c. 37; Human Fertilisation and Embryology Act of 1990; https://www.legislation.gov.uk/ukpga/1990/37
Human Fertilisation and Embryology (Research Purposes) Regulations	2001 No. 188; The Human Fertilisation and Embryology (Research Purposes) Regulations of 2001; https://www.legislation.gov.uk/uksi/2001/188/regulation/1/made

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Human Genetic Testing Act (HGTA)	SR 810.12; Bundesgesetz über genetische Untersuchungen beim Menschen (GUMG) vom 8. Oktober 2004; Federal Act on Human Genetic Testing (HGTA 2004) of 8 October 2004; https://www.admin.ch/opc/en/classified-compilation/20011087/index.html; the revised and by the parliament approved text (HGTA) is available via https://www.bag.admin.ch/bag/de/home/medizin-und-forschung/genetische-untersuchungen/aktuelle-rechtsetzungsprojekte1.html; The revised text will probably come into force beginning of January.
Human Research Act (HRA)	SR 810.30; Bundesgesetz über die Forschung am Menschen (Humanforschungsgesetz, HFG) vom 30. September 201; Federal Act on Research involving Human Beings (Human Research Act, HRA) of 30 September 2011; https://www.admin.ch/opc/en/classified-compilation/20061313/index.html
Human Research Ordinance (HRO)	SR 810.301; Verordnung über die Humanforschung mit Ausnahme der klinischen Versuche (Humanforschungsverordnung, HFV) vom 20. September 2013; Ordinance on Human Research with the Exception of Clinical Trials (Human Research Ordinance, HRO) of 20 September 2013; https://www.admin.ch/opc/en/classified-compilation/20121177/index.html
Loi sur la santé Canton Geneva	K 1 03; Loi sur la santé du 7 avril 2006; no English version; https://www.ge.ch/legislation/rsg/f/s/rsg_K1_03.html
Loi sur la santé publique Canton of Vaud	LOI 800.01, Loi sur la santé publique du canton de Vaud du 29 mai 1985 (LSP); no English version; http://www.drrybisarvandyke.ch/wp-content/uploads/LSP.pdf
Medcrime Convention	SR 0.812.41; CETS No. 211; Council of Europe Convention on the counterfeiting of medical products and similar crimes involving threats to public health of 28 October 2011; https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/211
Medical Products Licencing Ordinance (MPLO)	SR 812.212.1; Verordnung über die Bewilligungen im Arzneimittelbereich (Arzneimittel-Bewilligungsverordnung; AMBV) vom 14. November 2018; Ordinance on Licensing in the Medicinal Products Sector (Medicinal Products Licensing Ordinance, MPLO) of 14 November 2018; https://www.admin.ch/opc/en/classified-compilation/20180857/index.html
Ordinance on Human Genetic Testing	SR 810.122.1; Verordnung über genetische Untersuchungen beim Menschen (GUMV) vom 14. Februar 2007; no English version; https://www.admin.ch/opc/de/classified-compilation/20051790/index.html

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Ordinance on Organisational Aspects of the HRA (OrgO-HRA)	SR 810.308; Organisationsverordnung zum Humanforschungsgesetz (Organisationsverordnung HFG, OV-HFG) vom 20. September 2013; Ordinance on Organisational Aspects of the Human Research Act (HRA Organisation Ordinance, OrgO-HRA) of 20 September 2013; https://www.admin.ch/opc/en/classified-compilation/20121179/index.html
Ordinance to the Federal Act on Data Protection	SR 235.11; Verordnung zum Bundesgesetz über den Datenschutz, vom 14. Juni 1993; Ordinance to the Federal Act on Data Protection of 14. June 1993 (Status as of 16 October 2012); https://www.admin.ch/opc/en/classified-compilation/19930159/index.html
Patents Act (PatA)	SR 232.14; Bundesgesetz über die Erfindungspatente (Patentgesetz, PatG) vom 25. Juni 1954; Federal Act on Patents for Inventions (Patent Act, PatA) of 25 June 1954; https://www.admin.ch/opc/en/classified-compilation/19540108/index.html
Patient Act Zurich	813.13; Patientinnen- und Patientengesetz vom 5. April 2004; no English version; http://www2.zhlex.zh.ch
Patient Rights Ordinance Berne	BSG 811.011; Verordnung über die Rechte und Pflichten der Patientinnen und Patienten und der Gesundheitsfachpersonen (Patientenrechtsverordnung, PatV) vom 23.10.2002; no English version; https://www.belex.sites.be.ch/frontend/versions/346/embedded_version_content
Reproductive Medicine Act (RMA)	SR 810.11; Bundesgesetz über die medizinisch unterstützte Fortpflanzung (Fortpflanzungsmedizingesetz, FMedG) vom 18. Dezember 1998; The Federal Act on Medically Assisted Reproduction (Reproductive Medicine Act, RMA) of 18 December 1998; https://www.admin.ch/opc/en/classified-compilation/20001938/index.html
Stem Cell Research Act (StRA)	SR 810.31; Bundesgesetz über die Forschung an embryonalen Stammzellen (Stammzellenforschungsgesetz, StFG) vom 19. Dezember 2003; Federal Act on Research Involving Embryonic Stem Cells (Stem Cell Research Act, StRA) of 19 December 2003; https://www.admin.ch/opc/en/classified-compilation/20022165/index.html
Swiss Code of Criminal Procedure	SR 312.0; Schweizerische Strafprozessordnung (Strafprozessordnung, StPO) vom 5. Oktober 2007; Swiss Criminal Procedure Code (Criminal Procedure Code, CrimPC) of 5 October 2007; https://www.admin.ch/opc/en/classified-compilation/20052319/index.html
Swiss Code of Obligations	SR 220, Bundesgesetz betreffend die Ergänzung des Schweizerischen Zivilgesetzbuches (Fünfter Teil: Obligationenrecht) vom 30. März 1911 (Stand am 1. April 2020); Federal Act on the Amendment of the Swiss Civil Code (Part Five: The Code of Obligations)

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	of 30 March 1911; https://www.admin.ch/opc/de/classified-compilation/19110009/index.html
Swiss Criminal Code	CC 311.0; Schweizerische Strafgesetzbuch vom 21. Dezember 1937; Swiss Criminal Code of 21 December 1937; https://www.admin.ch/opc/en/classified-compilation/19370083/index.html
Swiss Federal Constitution (FedCst)	SR 101; Bundesverfassung der Schweizerischen Eidgenossenschaft vom 18. April 1999; Federal Constitution of the Swiss Confederation of 18 April 1999; https://www.admin.ch/opc/en/classified-compilation/19995395/index.html
The Biomedicine Convention; Oviedo Convention	SR 0.810.2; CETS 164; The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (The Biomedicine Convention, Oviedo Convention) of 1997; https://rm.coe.int/168007cf98
Therapeutics Products Act (TPA)	SR 812.21; Bundesgesetz über Arzneimittel und Medizinprodukte (Heilmittelgesetz, HMG) vom 15. Dezember 2000; Federal Act on Medicinal Products and Medical Devices (Therapeutics Products Act, TPA) of 15 December 2000; https://www.admin.ch/opc/en/classified-compilation/20002716/index.html
Transplantation Act	SR 810.21; Bundesgesetz über die Transplantation von Organen, Geweben und Zellen (Transplantationsgesetz) vom 8. Oktober 2004; Federal Act on the Transplantation of Organs, Tissues and Cells (Transplantation Act) of 8 October 2004; https://www.admin.ch/opc/en/classified-compilation/20010918/index.html
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Explanatory Report Pre-Draft HRA	Erläuternder Bericht des Eidgenössischen Departement des Inneren (Departement of Federal Affairs) zum Vorentwurf Bundesgesetz über die Forschung am Menschen (Humanforschungsgesetz, HFG) von Februar 2006
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Federal Council's Dispatch Additional Protocol Biomedicine Convention Transplantation	Curia 08.064; Botschaft Über die Genehmigung des Zusatzprotokolls Über die Transplantation menschlicher Organe und Gewebe zum Übereinkommen Über Menschenrechte und Biomedizin; BBl 2008 7951 (-7960)
Federal Council's Dispatch Art. 119 and PGD	Curia 13.051; Botschaft zur Änderung der Verfassungsbestimmung zur Fortpflanzungsmedizin und Gentechnologie im Humanbereich (Art. 119 BV) sowie des Fortpflanzungsmedizingesetzes (Präimplantationsdiagnostik) vom 7. Juni 2013; BBl 2013 5853 (-5964)
Federal Council's Dispatch Biomedicine Convention and Cloning	Curia 01.065; Botschaft betreffend das Europäische Übereinkommen vom 4. April 1997 zum Schutz der Menschenrechte und der MenschenwÜrde im Hinblick auf die Anwendung von Biologie und Medizin (Übereinkommen Über Menschenrechte und Biomedizin) und das Zusatzprotokoll vom 12. Januar 1998 Über das Verbot des Klonens menschlicher Lebewesen vom 11. September 2002; BBl 2002 271 (-336)

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[399] A "Federal Council's Dispatch" is a report to the Federal Assembly in which the Federal Council provides justification for a bill that it is submitting to the Assembly for consideration. If necessary, it includes comments on the individual provisions and provides information on certain aspects (legal background, points of view debated in the preliminary stages of the legislative process, planned implementation of the enactment, consequences of the enactment, etc.). Descriptions of the requirements in Art. 141 para. 2 Parliament Act (SR 171.10) BK, TERMDAT-Leitfaden, 2016, Appendix 4.1.

Federal Council's Dispatch StRA	Curia 02.083; Botschaft zum Bundesgesetz Über die Forschung an Überzähligen Embryonen und embryonalen Stammzellen (Embryonenforschungsgesetz, EFG) vom 20. November 2002; BBl 2003 1163 (-1277)
Federal Council's Dispatch Environment Protection Law	Curia 93.053; Botschaft zu einer Änderung des Bundesgesetzes Über den Umweltschutz (USG) vom 7. Juni 1993; BBI 1993 II 1445
Federal Council's Dispatch HGTA 2002	Curia 02.065; Botschaft zum Bundesgesetz Über genetische Untersuchungen beim Menschen vom 11. September 2002; BBI 2002 7361
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Federal Council's Dispatch PatA	Curia 05.082; Botschaft zur Änderung des Patentgesetzes und zum Bundesbeschluss über die Genehmigung des Patentrechtsvertrags und der Ausführungsordnung vom 23. November 2005; BBl 2006 155 (-186)
Federal Council's Dispatch Reproductive Medicine and Gene Technology	Curia 89.067; Botschaft zur Volksinitiative "gegen Missbräuche der Fortpflanzungs- und Gentechnologie beim Menschen" vom 18. September 1989; BBl 1989 III 989 (-1211)
Federal Council's Dispatch RMA 1996	Curia 96.058; Botschaft Über die Volksinitiative "zum Schutz des Menschen vor Manipulationen in der Fortpflanzungstechnologie (Initiative fÜr menschenwÜrdige Fortpflanzung, FMF)" und zu einem Bundesgesetz Über die medizinisch unterstÜtzte Fortpflanzung (Fortpflanzungsmedizingesetz, FMedG) vom 26. Juni 1996; BBl 1996 III 205 (-305)
Federal Council's Dispatch Transplantation Act	Curia 01.057; Botschaft zum Bundesgesetz Über die Transplantation von Organen, Geweben und Zellen (Transplantationsgesetz) vom 12. September 2001; BBl 2002 29 (-246)
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ISSCR Guidelines	International Society for Stem Cell Research (2021). ISSCR Guidelines for Stem Cell Research and Clinical Translation. Version 1.0, May 2021

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Votum Piller AB 1990	Curia 89.067. Gegen Missbräuche der Fortpflanzungs- und Gentechnologie beim Menschen. Volksinitiative. Botschaft und Beschlussentwurf vom 18. September 1989; BBI III, 989, AB S 1990 477 f.
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- BGE 146 V 297
- BGE 145 V 97
- BGE 145 V 116
- BGE 144 IV 254
- BGE 142 V 58
- BGE 138 II 513
- BGE 138 V 310
- BGE 136 V 117
- BGE 132 I 181
- BGE 131 I 166
- BGE 130 I 65
- BGE 130 I 16
- BGE 129 I 173
- BGE 127 I 145
- BGE 127 I 6
- BGE 126 I 112
- BGE 122 I 153
- BGE 119 Ia 460
- BGE 119 Ia 500
- BGE 115 Ia 234
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- Asiye Genç v. Rurkey, 24109/07 [2015]
- Parillon v. Italy, 46470/11 [2015; GC]
- Arskaya v. Ukraine, 45076/05 [2013]
- Mehmet Sentürk and Bekir Sentürk v. Turquie, 13423/09 [2013]
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- Roche v. United Kingdom, 32555/96 [2005]
- Vo v. France, 53924/00 [2004; GC]
- Gaskin v. United Kingdom, 10454/83 [1989]

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Chapter 6
Regulation of Genome Editing in Human iPS Cells: United States

Kathleen M. Sanzo

Abstract The United States (U.S.) has ever been, and still is, a world leader in the field of cell and gene therapies. This is mirrored by the US regulatory framework which fosters research on, as well as development, application and marketing of, cell and gene therapy (CGT) products without compromising their safety, efficacy and quality. The applicable framework is product-based, i.e. its rules apply independent of the processes used to manufacture the products. The legal basis for CGT product regulation is the Federal Food, Drug, and Cosmetic Act (FFDCA) which is complemented by a whole series of regulations and guidances issued by the Food and Drug Administration (FDA). In addition, CGT products may be eligible for certain FDA programs the purpose of which is to facilitate the development of, and access to, highly innovative products. In this regard, the program most applicable to CGT products is the 'Regenerative Medicine Advanced Therapy Designation' (RMAT) the purpose of which is to expedite review, and accelerate approval, of regenerative medicine products. FDA reviews and controls "Chemistry, Manufacturing, and Controls" (CMC) information submitted by the applicant for purposes of product approval. As regards biological data, de-identified data is not covered by U.S. data protection law. Data which has not been de-identified may be used for secondary research upon patient consent.

6.1 Introduction

6.1.1 History of Cell-based Product Regulation in the U.S.

The United States spends more money developing pharmaceutical and biotechnology drug products than any other country in the world, and currently is the leader in medical research and innovation of these products. Notwithstanding this significant advantage in public and private investment in medical research, the U.S. regulatory

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H.-G. Dederer, G. Frenken (eds.), *Regulation of Genome Editing in Human iPS Cells*, https://doi.org/10.1007/978-3-030-93023-3_6

and research communities have had challenges in fully exploring and exploiting research around certain types of gene and cell therapies because of the political environment in the U.S. surrounding this technology. Depending on which political party is in control of the Congress and White House, the legal restrictions on the scope of research on gene and cell therapy is more or less heightened. For example, after the U.S. Supreme Court decision in *Roe v. Wade*, 410 U.S. 113 (1973), legalizing a woman's right to abortion, the U.S. Department of Health, Education and Welfare placed a moratorium on funding by the U.S. Federal government for research using live human embryos.[1] In 1974, as a result of disclosures of ethical lapses in the Tuskegee Study, and desire to create ethical principles for biomedical research, the U.S. Congress extended a similar ban to include research on fetuses, before or after induced abortion.[2] In 1996, the U.S. Congress passed, and President Clinton signed, the Dickey-Wicker amendment to the National Institutes of Health ("NIH") appropriations bill, which prohibited federally-funded researchers from creating or causing harm to, or destroying, human embryos.[3]

In August 2001, President George W. Bush announced a policy on stem cell funding which banned federal funding for creating and research on embryonic stem cell lines created after that time, but allowed research on approximately 21 stem cell lines.[4] Further on June 20, 2007 President Bush signed an executive order directing the Department of Health and Human Services ("HHS") to conduct and support research on isolation, derivation, production, and testing of stem cells that are capable of producing all of the cell types of the body, i.e., to increase research and development of pluripotent stem cell lines.[5] The policy also continued the restriction on use of federal funding for research using human embryos and fetuses.

When President Barack Obama took office in 2009, he lifted the Bush ban, permitting researchers to use stem cell lines produced from embryos from In Vitro Fertilization ("IVF") procedures.[6] Currently, NIH has a detailed procedure in place to confirm the origin of a stem cell line in order to provide federal funding for research with the cell line.[7] NIH funding for stem cell research is only available if the stem cells were derived from women who voluntarily donated them from IVF treatment and agreed they could be used for research.[8] Note that because of the Dickey-Wicker Amendment which is still effective, U.S. federal funding cannot be

[1] 38 Fed. Reg. 3173 (1973); *see also* Reisman and Adams (2014), pp. 846–847 *citing* Wertz (2002), pp. 674–678.

[2] National Research Service Award Act of 1974, Section 214, Pub.L 93-340 (July 12, 1974).

[3] Section 509 of NIH Budget for 1996, Pub. L. 104-99, Section 128, 110 Stat. 26, 34 (Jan. 26, 1996).

[4] Snead (2005).

[5] Expanding Approved Stem Cell Lines in Ethically Responsible Ways, Executive Order 13435 (June 20, 2007).

[6] Removing Barriers to Responsible Scientific Research Involving Human Stem Cells, Executive Order 13505 (Mar. 9, 2009).

[7] National Institutes of Health, Guidelines for Human Stem Cell Research, July 7, 2009, *available at* https://stemcells.nih.gov/policy/2009-guidelines.htm.

[8] *Id.*

used to create new human embryonic stem cell ("hESCs") lines, only to conduct research on hESCs derived from private or state funding. Notwithstanding that stem cell research is politically charged, it continues to be the focus of substantial research dollars in the U.S. Moreover, the innovation which has occurred in development of induced pluripotent stem cells ("iPSCs") has relieved to an extent the tension between the political and ethical opposition to stem cell research and the public demand for new therapeutic treatments, especially for genetically-based diseases.

6.1.2 Current State of Cell and Gene Therapy Product Research in the U.S.

The stem cell market in the U.S. is projected to be worth $13 billion by 2025, growing over 10% per year.[9] Estimated U.S. federal funding in stem cell research in 2017 was only $1.58 billion,[10] so much of the anticipated investment will necessarily be through the pharma and biotech industries. At the end of 2018, there were 33 ongoing Phase III clinical trials of cell therapies and 16 of gene-modified cell therapies in the U.S.[11] Global investments in research in both kinds of cell therapy increased 64% over 2017.[11]

As of August 2019, NIH.gov, the NIH database in which all post-Phase 1 clinical trials conducted in the U.S. under an Investigational New Drug ("IND") application must be registered, listed approximately 5249 studies involving stem cells and 91 studies involving iPSC. Notably, many of the registered iPSC studies involve disease modeling objectives or optimizing iPSC development rather than therapeutic treatments.[12] The large difference in the number of registered studies of stem cells and iPSCs suggests continuing opportunities for iPSC-based product development, and a likely growing complexity of regulation as the U.S. Food and Drug Administration ("FDA") gains additional experience with these products.

In contrast to iPSC studies, there has been tremendous growth in cell and gene therapy product clinical trials, resulting from the increased experience and success in technologies for modifying cells and genes. According to FDA, there has been rapid growth in the number of gene therapy INDs. Between 1990 and 2019, the number of INDs for gene therapy trials rose from single digits to over 800 active INDs in 2019.[13] This increase has also resulted in the approval by FDA of five oncolytic and gene therapies since 2015,[14] including Imlygic (Sept. 2015), Kymriah (Aug. 2017), Yescarta (Oct. 2017), Luxturna (Dec. 2018), and most recently, Zolgensma

[9] MarketWatch (2019).

[10] America Recovery and Reinvestment Act, Pub. L 111-5 (Feb. 17, 2009).

[11] Albert (2020).

[12] Clinicaltrials.gov (as of August 25, 2019). Many of the studies registered in the NIH database on iPSCs are occurring outside the U.S.

[13] *See* U.S. Food & Drug Administration (2020b).

[14] Vatsan (2019).

approved in May 2019.[15] FDA reported that as of December 2019, four new additional gene therapy products were under review and it has accepted rolling submissions on at least two other products. The majority of new products have Breakthrough Therapy designation.[16]

FDA has noted that the increase in gene therapy trials also reflects a rapid growth in use of adeno-associated virus (AAV) (12%) and lentivirus (17%) vectors between 2017 and 2018, comparable to use of retrovirus (17%), adenovirus (14%) and plasmid (19%) vectors.[17] In addition, with the development of Chimeric Antigen Receptor ("CAR")-T cell technologies, CAR-T cell clinical trial investigations have substantially increased with 111 active INDs in 2018, with 32% directed to solid tumor cancers, and 68% directed to hematologic cancers.[18]

6.1.3 Current Regulation of iPSC-based Products in the U.S.

In the U.S., the FDA regulates both drugs and biologics under separate legal authorities. New drugs are regulated pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"). 21 U.S.C. § 355(b), whereas biological products are regulated under Section 351 of the Public Health Service Act ("PHSA"), 42 U.S.C. § 262. Generally cell and gene therapy products are considered as biologics in the U.S. A biologic is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment or cure of a disease or condition of human beings."[19] Notwithstanding regulation of biologics under the PHSA, the provisions of the Federal Food, Drug and Cosmetic Act (FFDCA) also apply to all biological products.[20] Biologic products must be demonstrated to be safe, pure, and potent, and the facilit(ies) in which they are manufactured, processed, packed or held must meet standards designed to assure the product continues to be safe, pure, and potent.[21] In addition to the statutory provisions, FDA has issued substantial regulations[22] and guidances for the testing and regulation of cell and gene therapy products.[23]

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[15] *See* U.S. Food & Drug Administration (2020a).

[16] *See* Silverman (2020).

[17] *Id.* at 5.

[18] *Id.* at 6.

[19] 42 U.S.C. § 262(i).

[20] 42 U.S.C. § 262(j).

[21] 42 U.S.C. § 262(a)(2)(c).

[22] 21 C.F.R. Part 600, et seq.

[23] For a full list of Cellular and Gene Therapy Guidances, *see* www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances (as of Jan. 2020).

To understand the regulatory framework for cell-based products, including iPSCs, it is important to understand the legal jurisdictional issues that have arisen in the U.S. around the use of stem cell-based products, which have impacted their investigational and treatment use. Part of this jurisdictional debate has arisen from the history of use of certain types of cell-based products such as autologous tissue products including bone marrow, skin grafts, umbilical cord blood in various medical procedures, and a recognition that the use of a patient's own cells and tissues for an individual patient's own medical needs did not require the full research, review and approval process required for traditionally manufactured drugs and biologics. Based on its authority in Section 361 of the PHSA to issue regulations to prevent introduction, transmission, or spread of communicable disease, FDA in 2005 established a separate regulatory framework for the limited use and safety of these types of human cells, tissues, and cellular and tissue-based products ("HCT/Ps").

Under 21 C.F.R. § 1271, HCT/Ps are defined as "articles consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."[24] Examples of these products include bone, ligament, dura mater, cornea, hematopoietic/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, and epithelial cells on a synthetic matrix. In order to be a HCT/P regulated product, the cell or tissue-product must meet the following criteria:

1. is minimally manipulated;
2. is intended for homologous use only, as reflected in the product labeling and advertising;
3. its manufacture does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving or storage agent, and assuming the addition of any agent does not raise new clinical safety concerns; and
4. *either* does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function, *or* if it has such an effect or is dependent on the metabolic activity of living cells, is intended for:
   - autologous use,
   - allogenic use in a first-degree or second-degree blood relative, or
   - reproductive use.[25]

As new stem cell technologies and uses have been further developed, and research has demonstrated many potential new uses of autologous stem cells, for example, to treat multiple sclerosis,[26] an increasing tension between FDA and medical practitioners has developed concerning the appropriate level of FDA

[24] 21 C.F.R. § 1271(d)(3).

[25] 21 C.F.R. § 1271.10.

[26] *See* National Institutes of Health (2020).

regulation of these products. FDA made it clear as early as 1998 that it considered adult stem cells of any origin (e.g., adipose, mesenchymal) for either autologous or allogenic use, to be biologics subject to the filing of a BLA if the cells were more than minimally manipulated.[27] Further, FDA adopted a broad definition of minimal manipulation, i.e., processing that does not alter the original relevant characteristics of the tissues relating to the tissue's utility for reconstruction, repair or replacement,[28] significantly restricting use of stem cells. Further, FDA defined homologous use as replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.[29]

The strength of FDA's legal theory of the basis for its regulation of adult stem cells was challenged in July 2012 in *U.S. v. Regenerative Sciences, Inc.*[30] in which the District Court for the District of Columbia examined whether and how the FDA can regulate mesenchymal stem cells. The plaintiff medical clinic asserted that the clinic has a right to use a patient's own cells for treatments of the patient, based on a physician's right to practice medicine, which is regulated in the U.S. under the individual states' licensing authorities for physicians. The court however rejected Regenerative Sciences' claim that the manufacturing process used by the company to expand the stem cells for their patients' treatment was minimal manipulation and, therefore, exceeded the types of uses that fell outside of FDA's regulation of biologics. Based on this judicial precedent, FDA has continued to assert its jurisdiction over medical clinics offering stem cell treatments in the U.S. through enforcement actions, including issuance of Warning Letters and court actions for restraining orders. These enforcement actions generally assert that the stem cell products created and used at these clinics do not meet the requirements for HCT/Ps under 21 C.F.R. § 1271, often because the cells are more than minimally manipulated, and the treatments offered are for diseases such as Parkinson's, Multiple Sclerosis, Chronic Obstructive Pulmonary Disease, diabetes, kidney failure and other serious diseases and conditions, which are not considered homologous use.[31] Because of the proliferation of stem cell clinics in the U.S., especially in Florida and California, FDA also has sought permanent injunctions in federal district court to stop them from offering stem cell product treatment. One California clinic which was the subject of a 2018

[27] Food and Drug Administration, Guidance for Industry, Guidance for Human Somatic Cell Therapy and Gene Therapy (Mar. 1998), *available at* https://www.fda.gov/media/72402/download, pp. 7–8. Food and Drug Administration, Guidance for Industry, Regulation of Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps): Small Entity Compliance Guide 4 (Aug. 2007), *available at* https://www.fda.gov/media/70689/download.

[28] 21 C.F.R. § 1271.3(f)(1).

[29] 21 C.F.R. § 1271(c)(3).

[30] *United States v. Regenerative Sciences*, Inc. No. 1:10-CV-1327, at 7 (D.D.C., July 23, 2012) (memorandum opinion) [hereinafter Memorandum Opinion]; *see United States v. Regenerative Sciences, LLC*, No. 10-1327 (D.D.C., July 23, 2012) (order).

[31] *See e.g.*, U.S. Food & Drug Administration (2019).

FDA enforcement action controlled over 100 medical site locations providing stem cell treatments.[32]

In June, 2019, Judge Ungaro in the U.S. District Court for the Southern District of Florida granted FDA's motion for summary judgment against U.S. Stem Cell Clinics, LLC in Florida, holding that the company had adulterated and misbranded the stem cell products it was administering, which were made from the each patient's own adipose tissue.[33] After hearing a description of the clinic's handling of the product to convert it from adipose tissue to stromal vascular fraction cell mixture (e.g., extraction, cell wash, treatment with a collagenase enzyme, centrifugation, straining, and combination with plasma or saline solution), the court concluded that the stem cells did not fall into the exemption for HCT/Ps to be used in the same surgical procedure under 21 C.F.R. § 1271 because the extracted cells did not remain essentially the same as the tissue from which it was extracted.[34] The court further found that because the cells were not promoted or used for homologous use, e.g., to perform the same basic function, the cells were not HCT/Ps, and therefore must be a biological drug subject to a biologics license application ("BLA").[35] Finally, the court dismissed the defendant medical clinic's arguments that the operation was regulated by the Florida Board of Medicine as the practice of medicine, stating that the regulation of the surgical procedure as practice of medicine would not preclude the stem cell product from being regulated by FDA as a drug.[36] The decision provided FDA with a significant victory, in that the court: (1) gave substantial judicial deference to FDA on how to regulate stem cells, (2) agreed that FDA could regulate them as either HCT/Ps or drugs, based on the amount of manipulation of the cells, (3) confirmed that the requirement that the cells be used for homologous use is a narrow concept, and (4) confirmed that the right of physicians to practice medicine under state law will not necessarily provide a legal basis on which to separately develop, market and use products considered within FDA's jurisdiction.[37]

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[32] U.S. Food & Drug Administration (2018).

[33] *U.S. v. U.S. Stem Cell Clinic, LLC, et al.,* Case No. 0:18-cv-61047-UU (S.D. FL June 19, 2019) (order granting FDA's motion for summary judgment).

[34] Food and Drug Administration, Guidance for Industry, Same Surgical Procedure Exception Under 21 C.F.R. 1271.15(b): Questions and Answers Regarding the scope of the Exception (Nov. 2017), *available at* https://www.fda.gov/media/89920/download.

[35] *U.S. v. U.S. Stem Cell Clinic, LLC, et al.*, Case No. 0:18-cv-61047-UU (S.D. FL June 19, 2019) (order granting FDA's motion for summary judgment) at 27, 29.

[36] *Id.* at ftn. 12.

[37] The Court dismissed the defendant's practice of medicine argument in a footnote, and therefore did not provide substantial analysis of the potential conflict between the physician's right to practice medicine which, for example, extends to prescribing FDA-approved drug products for unapproved uses, and FDA's jurisdiction. Historically, the enforcement mechanism for improper practice of medicine in the U.S. has been through state licensing enforcement actions and malpractice/negligence lawsuits brought by injured patients. Therefore, there will continue to be legal debate about where the line is between practicing medicine and manufacturing therapeutic stem cell drug products.

FDA was not as successful in a similar case in California. There, the U.S. district court held that the same surgical procedure exception under 21 C.F.R. § 1271 applies to the extraction of adipose tissue to isolate and make a stromal vascular fraction cell mixture as long as the re-implantation of the cells occurs in the same patient. The court concluded that the same surgical procedure exemption applies to this process as the cells for the adipose tissue were the target of the extraction, and the fact that the adipose tissue was a larger biological system that contained the cells did not change the analysis noting that the definition of HCT/P includes cells and tissue. Therefore, the court denied FDA's motion for summary judgment and ordered the parties to trial on the issue of whether the SVF[38] procedure alters the SVF cells.[39]

The 2019 and 2020 decisions demonstrate that federal courts do not agree on whether to grant complete judicial deference to FDA as to how to regulate the rapidly developing science and commercialization of stem cell products, including iPSC-based products.

6.2 Regulatory Requirements for Investigating and Seeking Approval for Gene/Cell Therapy Products

Consistent with its historical approach to regulation, the FDA has generally taken the view that its statutory authorities under the FFDCA and the PHSA are sufficiently broad and flexible to accommodate the regulation of new technologies. For example, when FDA first considered regulation of products that were manufactured using DNA/genetic engineering technology, FDA asserted that it did not need new legal authority because the Act allows it to regulate the product, e.g., the drug or biologic, rather than the process by which the drug or biologic is manufactured. Similarly, FDA would assert that the *ex vivo* modification of a patient's cells or genes outside of the patient's body is a processing operation, which creates a new drug product, which FDA can regulate under its existing legal authority. Consequently, FDA's approach to regulation of gene and cell therapy is that it will be based on a longstanding regulatory framework for drugs, biologics, and in some cases, medical devices, or a combination of them, with FDA identifying data, manufacturing requirements, and approval standards through specific regulatory guidances. To date, FDA has issued approximately fifteen guidances, with four specific guidances on cellular and gene therapy products (hereinafter "CGT").[40]

[38] Stromal Vascular Fraction.

[39] U.S. v. CA Stem Cell Treatment Center, Inc., No. EDCV 18-1005 JGB (KKx) (C.D. CA. Jan. 27, 2020).

[40] Food and Drug Administration website on Cellular and Gene Therapy Guidances, *available at* https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances.

Because of the increasing interest in and potential of CGTs, and with a mandate and resources from Congress, FDA has moved to streamline the product development and approval process, through use of the programs such as the Regenerative Medicine Advanced Therapy ("RMAT") designation.[41] The RMAT program was authorized under the 21st Century Cures Act, § 3033,[42] to expedite regenerative medicine products for serious or life-threatening diseases or conditions. This program, for example, allows sponsors to propose use of surrogate endpoints or intermediate clinical endpoints as the basis for approval, and to have product applications approved through the FDA's accelerated approval program. CGT products are also eligible for designation as a Breakthrough Therapy Product, a program which provides for intensive FDA guidance on product development, senior FDA official commitment to rapid review and approval, and additional flexibility relating to certain Chemistry, Manufacturing, and Controls ("CMC") requirements.[43]

Currently, the Center for Biologics Evaluation and Research ("CBER") in FDA has established the Office of Tissues and Advanced Therapies ("OTAT") to review and approve CGTs. This division reviews both INDs and BLAs for CGT products. Due to the increase in the number of gene therapy products, FDA announced in January 2019 that it planned to hire 50 additional reviewers for this division.[44]

As with the other investigational drug products, sponsors intending to conduct clinical trials with regenerative/gene therapy products must submit to FDA an IND, which includes the protocol for the proposed study, existing safety information from preclinical studies, and CMC information about the investigational product. The objective of the IND is to provide adequate information about the "...pharmacological and toxicological studies ...on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations [in humans]. The kind, duration and scope of animal and other tests required vary with the duration and nature of the proposed clinical investigations."[45] FDA recognizes that certain pharmacological principles may not apply to CGT products and therefore the traditional approaches to preclinical toxicity testing may not be appropriate or possible for them. Clinical trials are divided into Phases 1, 2, and 3, although the innovative/breakthrough status of most CGT/RMAT products often will allow sponsors to terminate early or proceed from a Phase 2 trial to approval, under one of FDA's expedited development pathways.

[41] *See* Food and Drug Administration, Guidance for Industry, Expedited Programs for Regenerative Medicine Therapies for Serious Conditions (Feb. 2019), *available at* https://www.fda.gov/media/120267/download.

[42] Twenty-first Century Cures Act, § 3033, Pub. L. 114-255 (2016).

[43] For a summary of these programs, *see* Food and Drug Administration, Guidance for Industry, Expedited Programs for Serious Conditions—Drugs and Biologics (May 2014), *available at* https://www.fda.gov/media/86377/download.

[44] *See* U.S. Food & Drug Administration (2020b).

[45] 21 C.F.R. § 312.23(a)(8).

6.2.1 General Recommendations for Preclinical Testing Programs for CGT

FDA CGT guidelines state that CGT preclinical program objectives should include:

- Establishment of biological plausibility;
- Identification of biologically active dose levels;
- Selection of potential starting dose level, dose-escalation schedule, and dosing regimen for clinical trials;
- Establishment of the feasibility and reasonable safety of the investigational product's proposed clinical route of administration;
- Support of patient eligibility criteria;
- Identification of physiologic parameters that can guide clinical monitoring, and
- Identification of potential public health risks (e.g., to the general public, caregivers, family members, close contacts, (co-workers, and intimate contacts).

FDA also provides general recommendations for all CGT product preclinical studies including:

- The product that is used in the definitive preclinical studies should be the product that is intended to be used in the human studies. FDA recognizes that in some cases, testing the actual intended product in animals may not be informative, and therefore alternative analogous products may be appropriate for the preclinical studies.
- The animal species chosen for the preclinical studies assessing bioactivity and safety should demonstrate a biological response similar to the investigational CGT product. FDA notes that non-standard test species may be useful and suggests that testing in more than one species may be necessary. To avoid mistakes in selecting animal species for testing, FDA recommends conducting *in vitro* and *in vivo* pilot studies prior to definitive preclinical studies to establish the biological relevance of the specific animal species used.
- Use of animal models of disease/injury to assess the CGT's activity and safety, including understanding and explaining the potential or known limitations of specific animal models and the ability of the animal model to mimic the target patient population, including similarities and differences of the pathophysiology of the disease in the animals and humans, and how the CGT product affects the disease/injury status.
- Use of proof-of–concept (POC) animal studies to show the feasibility and rationale for the use of the investigational CGT product in the targeted patient population, especially the potential benefit in view of the substantial inherent risks in CGTs. FDA expects POC studies to explore the pharmacologically effective dose of the product, the optimization of the route of administration and confirmation that the CGT reaches the target site, optimization of the timing of the product administration relative to the onset of disease, optimization of

dosing schedule, and characterization of the anticipated mechanism of action or hypothesized biological activity of the product.

- Toxicology studies to identify, characterize, and quantify the potential local and systemic toxicities, their onset, possible resolutions, and the effect of dose levels on toxicities. The FDA guidelines provide a list of primary and secondary considerations for study design. To the extent that there are animal species in which the CGT product is biologically active, it should be used in the toxicology studies. FDA also recommends that the toxicology studies mimic the proposed clinical trial design as closely as possible with regard to numbers of animals per gender that are appropriately randomized to each group, appropriate control groups, multiple dose levels, dosing schedule, route of administration, including as to the delivery device, multiple sacrifice time points to capture acute, chronic or delayed onset toxicities, and possible resolutions, safety endpoints that capture potential toxicities such as mortality, body weight, food/water consumption, and/or clinical pathology metrics, and other product specific measurement parameters, e.g., MRI[46] scans, cardiac or ophthalmic assessments.
- Consideration of product delivery approaches, including sufficient information to establish that the device necessary to therapeutic delivery is safe, and whether a device master file is being relied upon. CBER will consult with the Center for Devices and Radiological Health ("CDRH") to ensure the device information is adequate and complete.
- Certification of compliance of the preclinical studies with Good Laboratory Practices (GLPs) in 21 C.F.R. Part 58, to the extent possible. However, FDA acknowledges in its Guidance that because of the uniqueness of the products, unique animal models and lab personnel necessary to study CGT products, there may be a limited number of labs that can conduct preclinical studies and therefore any lack of GLP certification should be explained. It also notes that GLP compliance is not required for *in vitro* and *in vivo* pharmacology POC studies.[47]

6.2.1.1 Specific Preclinical Study Design Considerations for Cell Therapy Products

For preclinical studies of cell therapies, FDA also provides specific recommendations and considerations. For stem cell-derived products, FDA notes that the cells capacity for variable self-renewing replication through cycles of cell division and the capacity for differentiation into a variety of cells with specialized properties/functions must be considered, as well as the issues arising from the contamination of differentiated cells with undifferentiated cells. FDA also noted that sponsors need to

[46] Magnetic Resonance Imaging.

[47] Food and Drug Administration, Guidance for Industry, FDA Preclinical Assessment of Investigational Cellular and Gene Therapy Products (Nov. 2013), *available at* https://www.fda.gov/media/87564/download.

consider the ability to reach the site of treatment or concern with the cell product, the ability to deliver an absolute dose of cells to the target site, the availability of specific animals that will provide long term safety assessments, and potential immunogenicity of the animal to the human cell product.

Considerations for cell therapy preclinical study design include issues relating to the source of the cells, how they are manipulated *ex vivo,* the fate of the cells post-administration, including need for and success of engraftment. If engraftment is necessary for effectiveness, the study design will require that the animals be followed for a sufficient duration to evaluate *in vivo* cell survival, anatomic engraftment, and biologic activity.

Further, FDA notes the unique pathways for distribution of the cells throughout the host animal and requires the study to include methods to assess cell distribution, including through *in vivo* imaging using radio-isotope-labeled cells, genetically-modified cells structured to be easily identifiable, PCR and other detection methods. Whether and how the administered cells differentiate and integrate into other cell types and tissues is also required to be studied. Finally, FDA is and will continue to be concerned with the potential tumorigenicity of cell therapy products, and consequently will require animal studies to use the intended clinical product (not an analogous animal cell product) over a sufficiently long time to allow for potential tumor formation. FDA recommends that in designing these studies, sponsors consider the differentiation status, the extent of cell manipulation *ex vivo* and whether it is likely to encourage cell growth, the expressed transgene of the modified cells, the potential to induce or enhance tumor formation from subclinical host malignant cells, and the patient population.

6.2.1.2 Specific Preclinical Study Design Considerations for Gene Therapy Products

FDA reviews gene therapy products involving:

- Non-viral vectors (e.g., plasmids)
- Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus (AAV), retrovirus, lentivirus, poxvirus, herpes simplex virus (HSV))
- Replication-competent oncolytic vectors (e.g., measles, retrovirus, adenovirus, vesicular stomatitis virus, vaccinia)[48]
- Microbial vectors used for gene therapy (e.g., Listeria, Salmonella, E. coli, Bacteriophage)
- *Ex vivo* genetically modified cells

[48] Oncolytic vectors are defined by FDA as oncolytic viruses that have been genetically modified to carry an exogenous therapeutic gene. Oncolytic viruses which are not so modified are not gene therapies, and are not covered by this guidance. *Id.* at 23.

As with cell therapy products, FDA has substantial recommendations for preclinical study design of gene therapy products, including overall safety concerns resulting from immune response to the vector and toxicity from the components of the drug product, potential for insertional mutagenesis or oncogenicity, potential for germline transmission, and toxicity to family members from vector shedding. FDA identifies concerns for specific vectors including adeno-associated virus, retrovirus and lentivirus, pox virus, replication competent oncoviruses, and microbial vectors, and notes that biodistribution studies are required to understand the presence of the vector in target and non-target tissues or fluids, and the germline.

The timing and sequence of these preclinical tests should be discussed with FDA OTAT early in the development program to avoid costly and time-consuming mistakes in developing testing strategies. OTAT offers to meet with sponsors to discuss preclinical testing and data requirements in a pre pre-IND meeting, called the INTERACT Program (Initial Targeted Engagement for Regulatory Advice on CBER Products) to maximize testing and use of financial resources and minimize lengthy delays that can arise from unnecessary or inadequate testing.

6.2.2 Considerations for Early Stage Clinical Trials with CGT Products

In 2015, FDA finalized its regulatory guidance concerning early phase (Phases 1 and early 2) clinical trials of CGT products.[49] FDA's approach to early clinical trials with CGT products was influenced by substantial adverse consequences with prior CGT investigational products including subject death, development of leukemia in several patients, and brain and spinal cord tumor development in other patients. Further, FDA acknowledges that the potential for prolonged activity of the products, the possibility for immunogenicity, and the highly invasive aspect of product administration to the patient, create unique risks not generally present in small molecule and other biologic drug products. Finally, the lack of traditional preclinical data and the unique manufacturing requirements of CGT products, require additional consideration, planning, and response.

Unique aspects of CGT products which FDA identified as differentiating CGT products from traditional small molecule and biologic products in planning and implementing early phase clinical trials include:

- Need for long term follow-up to determine potential pervasive effects or effects which evolve over time (e.g., stem cells that proliferate and differentiate).
- High risk pre-treatment regimens prior to harvesting cells or before treatment, and invasive administration requirements that increase the overall risk of the therapy.

[49] Food and Drug Administration, Guidance for Industry, Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015), *available at* https://www.fda.gov/media/106369/download.

- The need to carefully review all devices that are used in connection with the CGT product delivery.
- Potential for immunogenicity that affects the safety or efficacy of the product or jeopardizes future therapies that may be needed for treatment of the disease or condition.
- For gene therapy products, the general uncertainty of how the gene is going to act, once administered, i.e., uncontrolled replication, turning other genes on and off, and shedding of vectors in a way that could infect others beyond the patient.
- Manufacturing complexities which may restrict dose, timing of dosing, and ability to control cell viability and potency, can create significant risk of not having adequate product at the necessary time of treatment, and/or not being able to accept product when it is available due to the patient's disease state.
- The need for study stopping rules which can be more quickly triggered to mitigate potential risk to subjects and to potentially allow prompt changes to the study protocol.

With regard to clinical trial design, as with other drugs, FDA expects early clinical trials to explore dose ranging and to establish, if possible, a maximum tolerated dose ("MTD"). However, if MTD is not possible, FDA would expect the study to establish a target range of exposure or the safety profile of feasible doses. Early trials would also be expected to address feasibility and reasonable safety of any special administration devices, or adjunctive treatments, and often to obtain preliminary evidence of activity of the CGT product. Further, to the extent patient selection for therapy will be based on genetic markers, the sponsor should consider whether biomarker assays will need to be developed, and how the timeline for development of the biomarker assay may affect the CGT product development timeline.

With regard to the patient population for early clinical studies, FDA notes that healthy volunteers generally will not be appropriate due to the high risk of the therapy. Further, it cautions that it may not be appropriate or a successful path to only enroll patients with severe or advanced disease or those with no other treatment options, as sicker patients will confound the ability to interpret the data and may not be able to withstand the toxicity of the product or the difficulty of the administration. If the indications are ones where future transplantation may be an option for the patient, sponsors need to determine if the use of the CGT product could compromise the patient's ability to later receive a transplant.

Sponsors should note that FDA is conservative with regard to CGT clinical trials for pediatric patients. FDA's regulations at 21 C.F.R. § 50.51 and § 50.52 require enhanced findings of direct personal benefit to the pediatric patients by the Institutional Review Board (IRB) overseeing the trial, and FDA has to be persuaded that it is not possible to obtain adequate safety data about pediatric patients from data on adult patients in order to include pediatric patients in trials for initial approval.

Other considerations unique to CGT products and clinical trials include how to establish the initial dose and proceed with dose escalation, the need for staggered administration to a smaller number of patients rather than treating all subjects in parallel or as recruited, to moderate the potential risk of the therapy, whether patient

cohort size may be restricted due to manufacturing limitations that restrict the amount of investigational CGT product that can be produced at any one time, operator training and proficiency for producing the CGT product, and documentation of the manufacturing procedures. If there are risks to caregivers from shedding cells or vectors, sponsors will be expected to address that risk as part of the clinical trial protocol.

Finally, because the effectiveness of CGT products is unknown, FDA expects sponsors to design into the clinical trial protocol significant follow-up procedures with all subjects to monitor adverse events. The duration of the follow-up is dependent on preclinical evidence of adverse events, but at least one year is expected.[50] For gene therapy products with vectors that are intended to integrate or that may have a latency period, FDA would expect sponsors to follow patients for 15 years. Clinical trial subjects must be informed through the informed consent document about the duration and scope of all necessary follow-up procedures and monitoring.

6.2.3 Manufacturing Considerations for Cell and Gene Therapy Products

In addition to the CMC controls identified by FDA for CGT products used in clinical studies, FDA has issued a number of guidances on specific CMC issues for clinical and finished CGT products. These include guidance for potency testing for CGTs,[51] recommendations for microbial vectors used for gene therapy,[52] testing recommendations for vector-based gene therapy products for replication competent retrovirus during manufacture and patient follow-up,[53] and the broadest of the guidances, CMC Information required for gene therapy INDs.[54] Although directed to gene therapy products, the guidance identifies the types of information about autologous or allogenic cells that must be provided in an IND, which would also be applicable to future iPSC-based products. These include:

[50] Food and Drug Administration, Guidance for Industry, Long Term Follow-Up After Administration of Human Gene Therapy Products (Jan. 2020), *available at* https://www.fda.gov/media/113768/download.

[51] Food and Drug Administration, Guidance for Industry, Potency Tests for Cellular and Gene Therapy Products (Jan. 2011), *available at* https://www.fda.gov/media/79856/download.

[52] Food and Drug Administration, Guidance for Industry, Recommendations for Microbial Vectors used for Gene Therapy (Sept. 2016), *available at* https://www.fda.gov/media/94200/download.

[53] Food and Drug Administration, Guidance for Industry, Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up (Jan. 2020), *available at* https://www.fda.gov/media/113790/download.

[54] Food and Drug Administration, Guidance for Industry, Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (Jan. 2020), *available at* https://www.fda.gov/media/113760/download.

- Materials used for collection of cells (including devices, reagents, tubing, and containers);
- Method of cell collection (i.e., standard blood draw or apheresis);
- Donor screening and testing protocols if using allogenic cells;
- Enrichment steps, if performed;
- Labeling and tracking of collected samples;
- Hold times for product; and
- Transportation conditions to and from the manufacturing facility.[55]

6.2.4 Approval of CGT Products

Cell, including iPSC-based, and gene therapy products are expected to meet the same data requirements for contents of a BLA as traditional biologic products. However, it is likely that many of the first to be reviewed iPSC products, like the gene therapy products approved to date by FDA, will be for rare diseases. Therefore, it is also likely that the product approvals will be the subject of FDA's various programs for more limited or alternative endpoints or expedited review with less data, with close oversight and assistance by FDA. Below is a brief summary of the various expedited approval programs and their criteria that currently exist for products intended for rare diseases or those addressing serious or life threatening diseases and/or unmet needs. FDA guidance on each of these programs should be consulted for full requirements.

6.2.4.1 Accelerated Approval: 21 C.F.R. § 314.601

- The Product must provide meaningful advantage over available therapies and demonstrate effect through **reasonably predictable surrogate endpoints** or an **intermediate endpoint that is measured earlier than irreversible morbidity or mortality**.
- The product must treat a serious condition, or address an unmet medical need.

6.2.4.2 Breakthrough Therapy Designation: 21 U.S.C. § 356(a)

- The product must have **preliminary clinical evidence** indicating the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints or be a qualified infectious disease product ("QIDP").
- The product must treat a serious condition.

[55] *Id.*

6.2.4.3 Fast Track Review: 21 U.S.C. § 506(b)

- There must be **non-clinical**, **clinical** or other data showing potential to meet unmet medical need, or be a QIDP.
- The product must treat a serious or life threatening disease or condition or address unmet need.

6.2.4.4 Regenerative Medicine Advanced Therapy Designation: 21 U.S.C. § 356

- The program which may be most applicable to iPSC-based products is the expedited program for RMATs.[56]
- The product must be a regenerative medicine, defined as cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using such therapies, except for HCT/Ps regulated under PHSA Section 361.[57]
- The product must be intended to treat, modify, reverse or cure a serious condition or disease.[58]
- The product must be supported by **preliminary clinical evidence,** including through possible use of surrogate or intermediate clinical endpoints, that it has potential for addressing unmet medical needs for such conditions.
- RMATs are eligible for participation in the other expedited review programs.

A product designation as a RMAT provides all of the benefits of the fast track and breakthrough therapy programs, including early interactions with senior FDA regulators, and the use of potential surrogate or intermediate endpoints to support accelerated approval. FDA expects the preliminary clinical evidence to be from clinical investigations specifically conducted to assess the effects of the therapy on the serious condition or disease, and notes that such investigations may not always be prospective clinical trials with a concurrent control, which may be particularly relevant to iPSC-based products.[59] Signaling its flexibility on this issue, FDA notes in its guidance that the evidence may come from clinical trials with historical controls, retrospective studies, or clinical case studies systematically collected from treating physicians.[60] The preliminary clinical evidence can come from studies

[56] Section 506 of the FFDCA, 21 U. S. C. § 356. The definition of serious disease or condition is a disease or condition associated with morbidity that has a substantial impact on day-to-day functioning.

[57] 21 U.S.C. § 356(g).

[58] *See* Food and Drug Administration, Guidance for Industry, Expedited Program for Regenerative Medicine Therapies for Serious Condition (Feb. 2019) *available at* https://www.fda.gov/media/120267/download.

[59] *Id.*

[60] *Id.*

outside of the U.S., but FDA emphasizes that the underlying studies should use the product that the sponsor intends to use in the clinical study in the U.S.[61] Products eligible for RMAT designation do not need to show that they offer a substantial improvement over available therapies. RMAT designation can be submitted at the time an IND is filed (if there is adequate preliminary clinical evidence at that time for example based on ex-US studies) or in an IND supplement if the data later becomes available.

FDA will respond to a RMAT designation request within 60 days, providing an explanation if the request is denied. If at some time during the development program for the product, it no longer meets the criteria for RMAT, the designation can be withdrawn for the product. FDA has indicated a willingness to withdraw designations, as it has done so several times for Breakthrough Therapy Products that became ineligible over the course of their development pathway.[62]

RMATs are eligible for accelerated approval based on surrogate or intermediate endpoints that are reasonably likely to predict long term clinical benefits or upon data obtained from a meaningful number of sites, including through expansion to additional sites. With regard to the latter basis, FDA acknowledges that a "meaningful" number is subjective terminology and will be dependent upon whether the evidence of efficacy is likely to be dependent on site specific or investigator-specific bias, such that the evidence does not provide a reliable basis on which to predict effect at other sites. If FDA grants approval on this basis, it suggests that sponsors would likely be required to provide post-approval clinical evidence through expansion of the trial to other sites. Other post-approval requirements could include patient registries, and patient follow-up programs. CBER strongly recommends that sponsors considering requesting RMAT consult early with CBER to discuss development plans and proposed clinical investigations.

6.3 Legal Protections for Patient Biological Data and Biospecimens

The principal law in the U.S. for the protection of individually identifiable health information is the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), Pub. L 104-91, as amended by the Health Information Technology for Economic and Clinical Health ("HITECH") Act of 2008, Pub. L 111-5, and the implementing Privacy and Security Rule at 45 C.F.R. Parts 160 and 164.[63]

The HIPAA Privacy Rule regulates the use and disclosure of protected health information ("PHI") by "covered entities," which are defined as health plans, health care clearinghouses, and health care providers who provide healthcare and patient

[61] *Id.*

[62] *See* Brennan (2019).

[63] For a full discussion of the HIPAA rule, *see* https://www.hhs.gov/hipaa/index.html.

treatment, and transmit health information in electronic form. Healthcare providers such as study investigators and hospitals who engage in clinical research or provide patient care are covered by the rule. However, study sponsors such as pharma companies are generally not subject to HIPAA as they do not meet the definition of a "covered entity."

PHI is defined as "individually identifiable health information" that is held or transmitted by a covered entity in any form, paper or electronic.[64] De-identified data, which is stripped of eighteen separate common identifiers such as name, address, date of birth, and social security number, is not considered PHI.[65] Genetic information, defined as information with regard to an individuals' genetic tests, the tests of family members of such individual, and the manifestation of diseases or disorders in family members of such individual, arising from tests or biosamples collected as part of medical research, is considered PHI, and thus has the protections of HIPAA, pursuant to the Genetic Information Nondiscrimination Act ("GINA") of 2008, Pub. Law 110-233, 122 Stat. 881.[66] Notably, biospecimens not identified with PHI are not protected by HIPAA.

Under the HIPAA Privacy Rule, covered entities may not use or disclose PHI except as permitted or required. Only two types of disclosures are required: when a patient requests his/her own PHI and when the Secretary of HHS requests PHI for audit or other enforcement purposes. All other disclosures, including those that may be required by other federal or state laws (e.g., FDA pharmacovigilance reporting or public health reporting statutes), are considered "permitted," by the Privacy Rule.[67] For example, covered entities are permitted to access, use, and disclose PHI for the purposes of treatment, payment, and health care operations.[68] As a result, many disclosures of PHI, including those related to treatment, payment, and health care operations, require no authorization by the patient. Written "authorizations" by patients are required for uses and disclosures of PHI that are not otherwise permitted or required.

Therefore, to the extent biological data (e.g., results of a DNA test) is associated with a patient, and not de-identified, it is protected by HIPAA, and can only be used consistent with the patient's approval, or for a permitted use. Other uses of the data, for example, for secondary research would not be allowed, without the patient's authorization.

There are however fewer restrictions on secondary uses of biological samples, and in particular, there is an absence of one coherent U.S. federal standard with regard to when and how to obtain patient consent[69] for secondary research uses of

[64] HIPAA, § 1171(5), 45 C.F.R. § 160.103.

[65] *See* 45 C.F.R. § 164.502 (d) and § 514 (a) and (b).

[66] 78 Fed. Reg. 5566, 5659 (Jan. 25, 2013).

[67] 45 C.F.R. § 160.103.

[68] 45 C.F.R. § 164.502(e).

[69] Human Subjects are protected in the US under both the Common Rule for federally funded research at 45 C.F.R. Part 46, and FDA's regulations at 21 C.F.R. Part 50, which applies to research conducted to support a regulatory filing such as an NDA or BLA.

biospecimens. In January 2017, HHS issued a final rule updating the requirements for the protection of human subjects for U.S. federally funded research (known as the "Common Rule"), which was principally directed to changes to rules relating to informed consent for human subject research. However, one of the issues that was debated prior to the final rule was the handling of biospecimens, and when their use requires patient consent. Under the proposed rule, because patient identity can be gleaned from a biosample, it was proposed that all biospecimens would always be considered identifiable. However, in public comments there was a significant concern raised by the research community that such treatment would substantially impede medical research. Therefore, the final federal rule continues to consider use of sufficiently de-identified biospecimens as not human subject research, and therefore not requiring patient consent for their secondary use.[70] Although private institutions and industry not using federal research money grants are not required to abide by the Common Rule, many generally do follow it. In 2018, the HHS Advisory Committee on Human Research Protections (SACHRP) provided a series of Q and As about using biospecimens and tissues for secondary research.[71] These include:

- If the biospecimen is not individually identifiable, i.e., is not known or readily ascertainable by the investigator, study team, or the study sponsor, the sample is considered de-identified and there is no restriction on its use or need to obtain patient consent or authorization. The research with the biospecimen is also not considered human subject research.
- If the biospecimen is coded (i.e., a number, symbol or combination has replaced identifying information that could be used to ascertain the identity of the subject, and a key to the code exists), it is considered de-identified if neither the investigator, study team, nor the study sponsor can link the specimen to the subject from whom the specimen was collected, either directly or indirectly through the coding systems, and there is no need for consent or authorization. Research with these biospecimens is also considered not human subject research.
- If there are questions about whether prior patient consent was sufficiently broad to allow the proposed biospecimens to be used, an IRB or Ethics Committee should review the consent provided, the nature of the proposed research, whether the research imposes new or significantly greater risks (including to privacy) not described in the original consent, and whether there are known concerns by the study population to the proposed research.
- If the original consent specifically prohibited the proposed secondary research use, the research is presumed not allowed.[72]
- If a biospecimen can be linked to an individual, consent for its secondary use will generally be required.

[70] 82 Fed. Reg. 7149 (Jan. 19, 2017).

[71] U.S. Department of Health & Human Services (2018).

[72] *See* U.S. Department of Health & Human Services (2011).

- If the specimen is being used to research and develop *in vitro* diagnostics under FDA regulations, special regulations apply, as FDA defines human subject research more broadly than other federal statutes.[73] In addition, FDA's regulations on protection of human subjects have not yet been reconciled with the Common Rule, so there are slight differences.

6.4 Legal Developments Relating to Ownership of Biospecimens

In the U.S., there have been a series of court decisions concerning the ownership of biospecimens. In *Moore v. Regents of the University of California, et al.*, 51 CAL 3rd 120,271 Cal Rptr. 146, 752 P2d.429 (1991), a state court ruled that individuals do not have an ownership interest in their cells after the cells have been removed from their body, and do not have the right to a share in profits derived from products made from the cells. This decision was precedent for many years, and in part, provided a level of certainty to the pharma and biotech industries that their research investment in cell-based products would not be threatened by later-claims of ownership of cells or other biospecimens used in drug development.

More recently, in 2003, in *Greenberg v. Miami Children's Research Institute, Inc.,* 264 F. Supp 1064 (S.D. FL 2003), a federal district court in Florida ruled that individuals who provided tissue samples from which a genetic assay was developed did not own their tissue samples. Again, certainty was provided to the research community that development of IVDs[74] or other biomarker tests or assays would not be threatened by claims of ownership from tissue or cell donors.

Finally, in 2008, the U.S. Supreme Court declined to review a lower appellate court decision, *Washington University v. Catalona*, 490 F.3d 667 (8th Cir. 2007), that held that individual donors of biospecimens do not retain an ownership interest in the specimens, nor can they direct or authorize the transfer of those samples to a third party. In that case, a researcher, and his employer, Washington University in St. Louis, were disputing who owned a biospecimen repository of thousands of samples created by the researcher and used to develop the PSA[75] bioassay for prostate cancer. The researcher had proposed to provide free access to the samples with a researcher at another institution, while the University claimed ownership and demanded that the second institution pay for the samples. When the lead researcher decided to move to a different academic research institution, Washington University sued the researcher to prevent the transfer of the samples, claiming the researcher and the tissue donors had no right to the biospecimens and no right to direct the disposition of them. The Court held that Washington University, owned the

[73] *See* 21 C.F.R. § 812.3(p).

[74] In Vitro Diagnostics.

[75] Prostate Specific Antigen.

biorespository because the patients had donated the samples, notwithstanding language in the informed consent that allowed patients to withdraw their consent for use of the samples. *Id.* Consequently, in the U.S., the use of biospecimens for secondary research use generally will be unrestricted, assuming they are sufficiently de-identified or properly coded, and the consent form for the study in which they were collected does not specifically prohibit further research with them. Further, the biospecimen repository can be owned by multiple parties, other than patients, involved in research.

6.5 Future of Germline Intervention Therapeutics in the U.S.

As CRISPR and related technologies continue to develop and provide an effective and reliable method for editing genes, the U.S., Congress will direct or require NIH and/or FDA to define the principles surrounding the use of these technologies, and the ethical lines defining the context for their use. In 2019, as a response to reports of a Chinese researcher genetically editing several human embryos, several U.S. Senators introduced a resolution calling for global collaboration in developing guidelines for the use of gene editing technologies in the context of reproduction.[76] Although the resolution was not adopted, it demonstrates the concern in the U.S. with regard to unregulated gene editing, and the unintended consequences it can produce, potentially leading to a catastrophic public health crisis. It is also likely that academic medical institutions involved in researching and testing gene editing technologies will subject them to significant oversight by IRBs, and institutional risk officers.

6.6 Conclusion

The U.S. pharma, biotech, and regulatory authorities are rapidly gaining experience in the development and testing of CGT products. Although development of iPSC-based investigational products has not been as rapid as other gene and cell therapy products, it is only a matter of time before iPSC product clinical trials are conducted. Progress in other parts of the globe will spur innovation and urgency in the U.S. and put pressure on the FDA to find pathways to approve these products.

Greater challenges however could lie in the manufacturing process for these products, and their delivery to patients, as the current U.S. manufacturing infrastructure is built for mass produced drugs at a single site, using a national distribution system. The FDA inspection and regulatory review process is also built around the

[76] *See* United States Senator for California (2019).

concept of centralized manufacture, so modification to the regulatory system will also be necessary. Bedside manufacture of treatments could be a fundamental disruptor to the current drug and biologic supply chain.

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Chapter 7
Regulation of Genome Editing in Human iPS Cells: Japan

Hanayuki Okura and Akifumi Matsuyama

Abstract Regenerative medicine based on genome-edited induced pluripotent stem cells (iPS cells) is regulated under the Pharmaceutical and Medical Device Act or the Regenerative Medicine Safety Act in Japan. The Pharmaceutical and Medical Device Act (PMD Act) regulates regenerative medicine products by classifying them as cellular products and restricts their availability on the market by requiring prior biological license approval for any entity that wishes to place these products on the market. The Regenerative Medicine Safety Act regulates regenerative medicine products by classifying them as techniques that are used by doctors who deliver these medications to patients undergoing procedures such as organ transplantation, and these medicinal products are made available to doctors in a manner that is similar to that of the hospital exemption practices of the EU. Genome-edited-iPS cell-derived medicinal products and medicinal techniques should be regulated under these acts correspondingly. Assuming that the genome-edited iPS cell-derived regenerative medicine products should be submitted for use in clinical trials under the PMD Act, they will be reviewed in a manner similar to that of advanced therapy medicinal products (ATMP) in the EU or biologics in the US. If doctors are to conduct such trials, the trial protocols should be reviewed by a governmental review committee that assesses highest risk medical techniques. This system resembles that of organ transplantation in regard to its philosophy. The major difference between the EU and the USA is that in Japan there are two tracks for clinical application: one involves pharmaceutical regulation and the other involves organ/tissue/bone marrow transplantation regulation. Although there are two tracks for clinical application, in either case the genome-edited-iPS cell-derived cells should be evaluated in regard to mosaic phenomena, off-target effects, and on-target insertion/deletion abnormalities that affect the genomic structure. These evaluations should occur in addition to the conventional regulatory requirements.

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H.-G. Dederer, G. Frenken (eds.), *Regulation of Genome Editing in Human iPS Cells*, https://doi.org/10.1007/978-3-030-93023-3_7

7.1 Introduction

7.1.1 *Support Programs and Implementation Schemes in Different Countries*

Japan is recognized as a leader in the clinical application of iPS cells (iPSCs); however international competition in the field of regenerative medicine has been intensifying, as clinical trials involving ES cells (ESCs) have already been conducted in other countries. Additionally, the realization of regenerative medicine is currently being extensively promoted in these countries. In the United States, the regenerative medicine-related government budget is approximately 9% of the National Institutes of Health (NIH) budget. It was allocated in 2018 to the category of "regenerative medicine" and "stem cells", categories that possess a large degree of overlap. Based upon the continued existence of a large number of unmet medical needs, in 2016, the "21st Century Cures Act" was enacted.[1] In addition, the Regenerative Medicine Advanced Therapy (RMAT) program was implemented which allows for accelerated approval of research support at the state level. The largest example of this occurred in the state of California, where in 2017 the California Institute for Regenerative Medicine (CIRM) was founded based on a grant of US$390 million.[2] In recent years, support for clinical research has been strengthened. In the EU, the Horizon 2020 program has been set up a portion of which is dedicated to regenerative medicine.[3]

The UK has announced "A Strategy for UK Regenerative Medicine"[4] as its overarching regenerative medicine strategy, and the government has established a cell therapy catapult and multi-year regenerative medicine platform termed "UK Regenerative medicine platform UKRMP".[5] These two frameworks will be later integrated into the Cell and Gene Therapy Catapult (CGT Catapult),[6] which will function as a research and development center for cell and gene therapy. At the University of Toronto in Canada, various stakeholders were gathered from basic research and industrial fields to construct an eco-system that was set up as the Centre for Commercialization of Regenerative Medicine (CCRM) to promote the commercialization of regenerative medicine.[7]

The Fraunhofer-Gesellschaft[8] in Germany is the largest applied research institution in the EU. It has initiated technology transfer procedures to promote the

[1] 21st Century Cures Act. https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act.

[2] California Institute for Regenerative Medicine. https://www.cirm.ca.gov/.

[3] Horizon 2020. https://ec.europa.eu/programmes/horizon2020/en.

[4] Medical Research Council (2012).

[5] UK Regenerative medicine platform UKRMP. https://www.ukrmp.org.uk/.

[6] Cell and Gene Therapy Catapult. https://ct.catapult.org.uk/.

[7] Centre for Commercialization of Regenerative Medicine. https://www.ccrm.ca/.

[8] Fraunhofer-Gesellschaft. https://www.fraunhofer.de/en.html.

industrialization of applied research involving regenerative medicine. Additionally, in recent years, China has advanced rapidly in the field of regenerative medicine, and these advances have been facilitated by the competitive funding provided by the "national key research and development plan"[9] that invests in focused areas of regenerative medicine.

Various standardization organizations have been established to facilitate the standardization and international harmonization of pluripotent stem cell repositories, including those containing iPS cells, that provide the raw materials used in regenerative medicine and their final cell-processing products. International discussions regarding this topic have occurred, and the International Stem Cell Initiative (ISCI)[10] has released proposals regarding the quality assessment of pluripotent stem cells and the potential tumorigenicity of these cells.[11] To allow for standardization and international harmonization from the level of the cell bank to the level of clinical iPS applications, the Global Alliance for iPSC Therapies (GAiT)[12] was created which released human iPS guidelines detailing the quality standards for use of these cells in clinical applications.[13]

7.1.2 Scientific Research Trends Within the Stem Cell Field (Fig. 7.1)[14]

The number of manuscripts that incorporate the use of ES cells has steadily increased up until 2007. In 2006, murine iPS cells were reported for the first time by Prof. Yamanaka and others, and human iPS cells were reported in 2007, ultimately leading to increased stem cell research activity that included the investigation of ES cells. The number of manuscripts examining pluripotent stem cells has increased sharply since 2007, and in 2017, the number of papers detailing the use of iPS cells was as high as the number of manuscripts that incorporated the use of ES cells. This indicated that iPS cells were finally widely accepted by the scientific community to be representative of pluripotent stem cells.

Based on a comparison of the number of published papers in each country (Fig. 7.2), the United States published 42% of the total papers, while Germany, Britain, and Japan were also major contributors. Japan published the fourth largest number of research papers examining ES cells and in contrast, Japan is second only to the USA in published reports involving the use of iPS cells.

[9] Federal Office of Public Health (2018).

[10] The International Stem Cell Initiative. http://www.stem-cell-forum.net/initiatives/isci/.

[11] International Stem Cell Initiative (2018).

[12] Global Alliance for iPSC Therapies. http://www.gait.global/.

[13] Sullivan et al. (2018).

[14] Negoro et al. (2017).

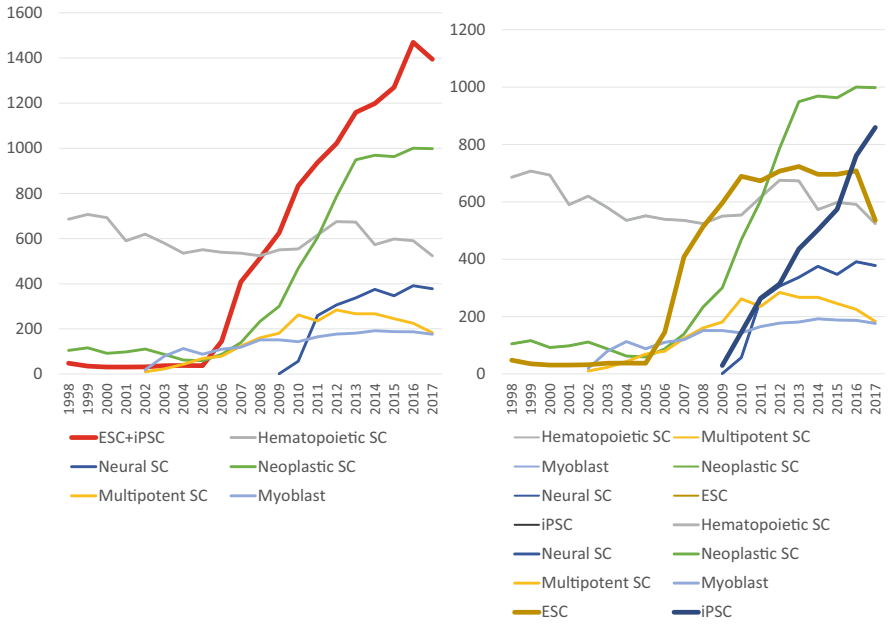

Fig. 7.1 Global trends in research using PSCs (Negoro et al. 2017)

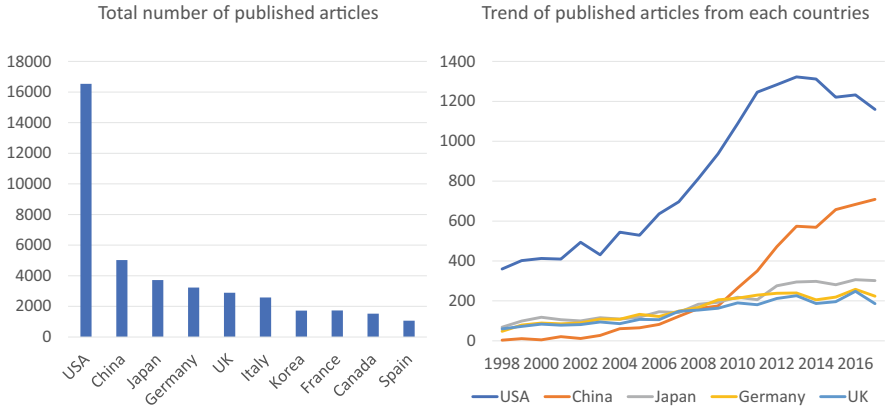

Fig. 7.2 Number of published papers from each country (Negoro et al. 2017)

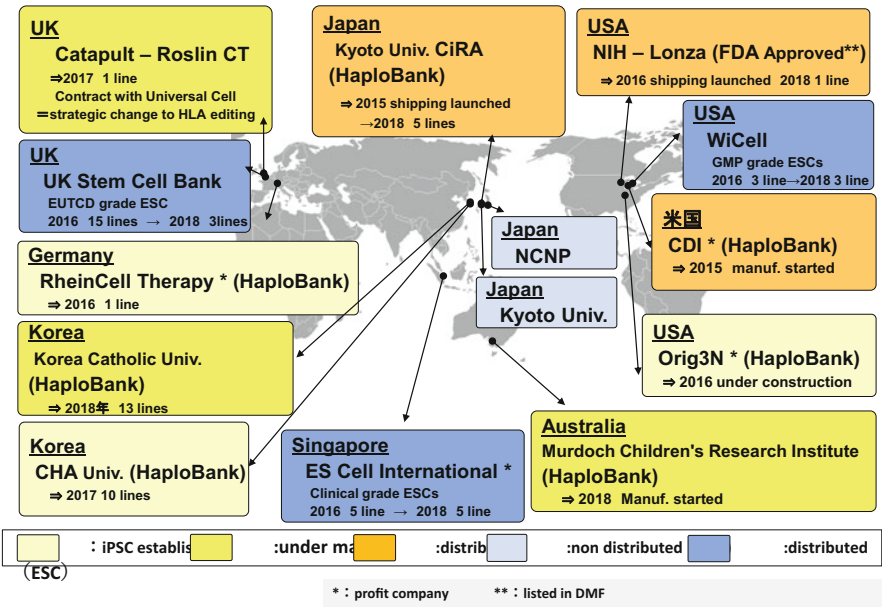

Fig. 7.3 Clinically usable iPSC/ESC banks throughout the world (Dec 2018)

7.1.3 Bank for Clinically Applicable Pluripotent Stem Cells (Fig. 7.3)

A human ES cell bank for clinical use has been established through a collaboration involving the UK Stem Cell Bank in the UK, WiCell in the United States, and the Kyoto University Institute for Virus and Regenerative Medicine in Japan. The UK Stem Cell Bank can release 3 cell lines, WiCell can release 3 cell lines (Dec. 2018), and Kyoto University can also release a number of cells. ES Cell International, Inc. is a for-profit company located in Singapore that has announced that they can offer 5 lines of clinically applicable ES cells. In regard to clinically applicable human iPS cell banks, the Kyoto University iPS Cell Research Institute (CiRA) and the US NIH offer cell banks as non-profit organizations.

CiRA has promoted the HLA[15] homozygous iPS cell bank, and they are able to provide seven strains as of June 2019. In contrast, the NIH iPS cell bank for clinical application has not matched the HLA type, and only one strain is available as of June 2019.

Commercial iPS cell banks for clinical use may become available soon through the US Cellular Dynamics International (CDI) and UK CGT Catapult-Roslin Cells groups. In recent years, it has been reported that the CGT Catapult-Roslin Cells

[15] Human Leucocyte Antigen.

group has contracted with Universal Cells Inc. in the United States, and these groups have switched to a strategy that involves the use of iPS cells modified by HLA for genome editing. Overall, in terms of clinically useful iPS cells, CiRA is believed to be one step ahead. The NIH and CDI have only just begun to distribute cells.

7.1.4 Launch Status of Regenerative Medicine Products (Fig. 7.4)

In Japan, several regenerative medicine products have received biological license approval. JACE® is an autologous, epidermal-derived cell sheet intended for the treatment of severe burns, pigmented nevus, and epidermolysis bullosa. JACC® is an autologous, cartilage-derived tissue intended for the treatment of cartilage disease affecting the knee joint, and TemCell-HS® is allogeneic bone marrow-derived mesenchymal stem cell treatment intended for alleviating acute graft-versus-host disease (GVHD) after bone marrow transplantation. Kymriah® is an *ex vivo* gene therapeutic product used for the treatment of B cell leukemia and lymphoma (CAR-T cell therapy) that has received approval for production and marketing. Heartsheet® is an autologous, skeletal muscle-derived cell sheet-based treatment for severe heart failure, and Stemilac® is an autologous, bone marrow-derived mesenchymal stem cell-based treatment intended for use in treating subacute spinal cord injury. Heartsheet® and Stemilac® have both received conditional and term-limited approval. In Asia, South Korea has approved a large number of products (23 products). Japan, China, and India have also approved several products. In the US, 18 products have been approved, and three of these products are related to immunotherapy. In North America, 4 products have been approved in Canada. In the EU, there are 8 products that have been approved by the regulatory authority EMA (European Medicines Agency), and 5 of these products are related to gene therapy. The EMA system is closely related to the advanced health care system of Japan, where regenerative medicine products can become available within the hospital exemption framework. In Germany and the UK, 9 products and 1 product, respectively, have become available on the basis of the hospital exemption. In regard to the global status of "regenerative medicinal products", skin (including the mucous membranes, such as the cornea) and the cartilage regenerative products account for the majority of currently available products. The primary culture technology of skin and cartilage is well established, and the technologies have been thoroughly adapted for clinical use. Osteoarthritis of the knee joint is the main target of the bio spin-off companies, as there is a large market for these treatments.

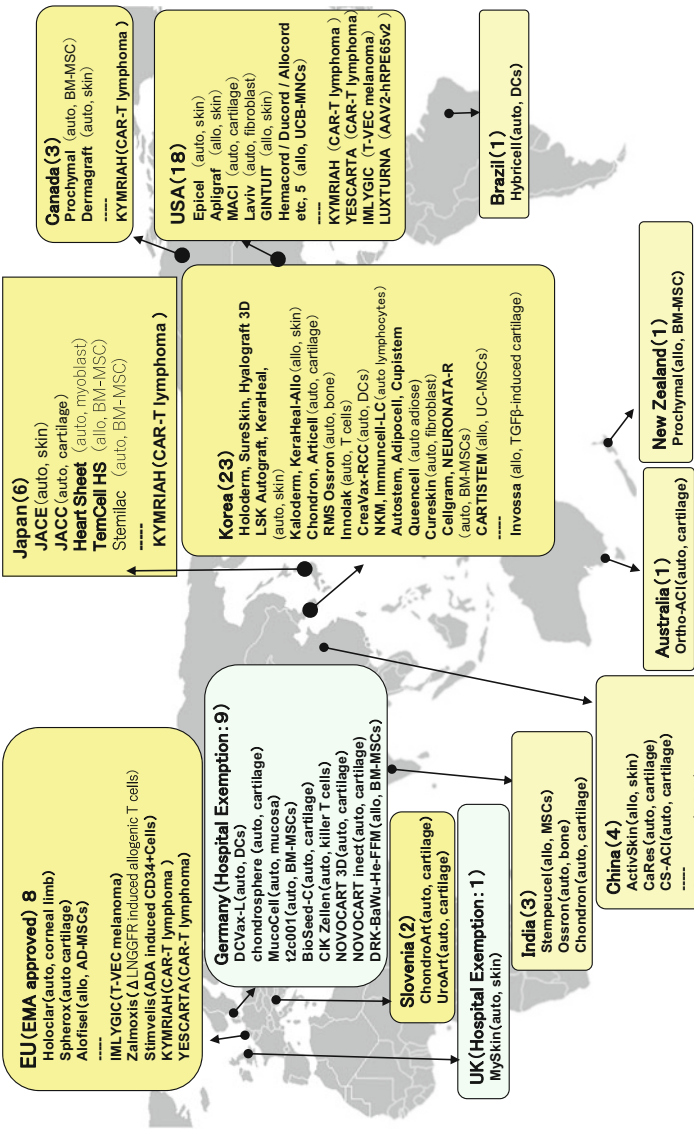

Fig. 7.4 Tissue-engineered medicinal products throughout the world (Sep 2019)

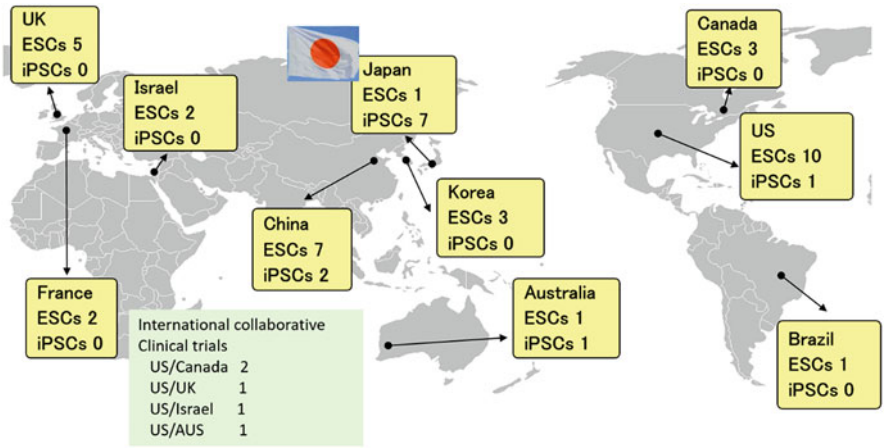

Fig. 7.5 Clinical trials using PSCs-derived clinical products

7.1.5 Status of Clinical Trials Using Pluripotent Stem Cells

Through the end of 2019, a large number of clinical trials incorporating pluripotent stem cells, ES cells, and iPS cells have been launched world-wide. Trials in the United States, UK, France, China, South Korea, Australia, Israel, Brazil, and Japan account for a total of 41 protocols (Fig. 7.5).

Thirty protocols have been implemented using ES cells, and 11 implemented protocols use iPS cells. Clinical trials using iPS cells have been conducted in Japan, China, Australia, and the USA. In Japan, seven clinical trials are currently underway involving the use of iPS cells to treat age-related macular disease with regenerated retinal pigment epithelial cells (2 protocols), Parkinson's disease, spinal cord injury, ischemic heart disease, corneal disease using corneal epithelial cells derived from iPS cells, and refractory anemia using platelets. Cartilage regenerative products using iPS cells for orthopedic disease, photoreceptors derived from iPS cells for the treatment of age-related macular disease, and corneal endothelial cells for the treatment of corneal disease will be launched by 2020. In contrast, there is only one clinical trial using ES cells to treat urea cycle disorders in Japan. Unfortunately, the protocol has been approved as IND for 2 years, and no patients have been enrolled. The reason for this remains unknown.

Of the 41 clinical trials using pluripotent stem cells, 20 of these are examining the use of these cells to treat retinal degenerative macular diseases such as age-related macular degeneration. Twenty-eight protocols (68%) target retinal diseases (20 protocols), while only 4, 1, and 3 protocols target Parkinson's disease, amyotrophic lateral sclerosis (ALS), and spinal cord injury, respectively (Table 7.1).

In these protocols, iPSC-derived regenerative medicinal products could be used for tissues that are protected blood-brain barriers and for immuno-escape organs. It is therefore considered essential to overcome immune rejection. Three clinical trials for

Table 7.1 Clinical trials using PSC-derived clinical products (Dec 2019)

	hESCs	iPSCs	hPSCs
Total	30	11	41
Retinal disease	17	3	20
Parkinson's disease	2	2	4
ALS	1	0	1
Spinal cord injury	2	1	3
Type I DM	3	0	3
IHD	1	2	3
GVHD	0	1	1
Meniscus injury	1	0	1
Ovary insufficiency	1	0	1
Corneal epithelium	1	1	2
Platelet	0	1	1
Congenital hyperammonemia	1	0	1

type 1 diabetes have been conducted using ES cells, and for these trials, it is important to evade immune rejection. Based on this, it is difficult to develop immuno-isolation devices for isolating transplanted islet cells. Recruitment of new subjects has been suspended due to device issues for all protocols. As mesenchymal stem cells (MSCs) have already been applied in medical practical, trials for inducing differentiation of pluripotent stem cells into MSCs and their further clinical development are also progressing. The Australian company Cynata has completed international clinical trials in Australia and the United Kingdom using iPS cell-derived MSCs to treat graft-versus-host disease. Additionally, two clinical trials using ES cell-derived MSCs for the treatment of cartilage regeneration and ovarian failure have been conducted in China. For clinical trials using pluripotent stem cells to treat ischemic heart disease, ES cell-derived cardiomyocytes were used in France and iPSC-derived cardiomyocytes were used in Japan. For clinical trials examining the corneal epithelial stem cell exhaustion disease, China has one protocol that uses ES cells and Japan has one protocol that uses iPS cells. A number of for-profit enterprises have been established in various countries to promote the clinical implementation of promising iPS cell research results. Examples include Platelet BioGenesis in Massachusetts (Harvard University), BlueRock Therapeutics in New York, and Fate Therapeutics in California (Fig. 7.6).

7.1.6 Clinical Trials and Clinical Applications

For regenerative medicine that utilizes stem cells, several clinical trials using somatic stem cells such as mesenchymal stem cells have been conducted in Japan, and certain products have already been approved for manufacture and sale as regenerative medicinal products. The safety of these products has been confirmed in corneal endothelial cell transplantation for bullous keratopathy and synovial stem cell transplantation for meniscal injury, and a number of findings highlighting the

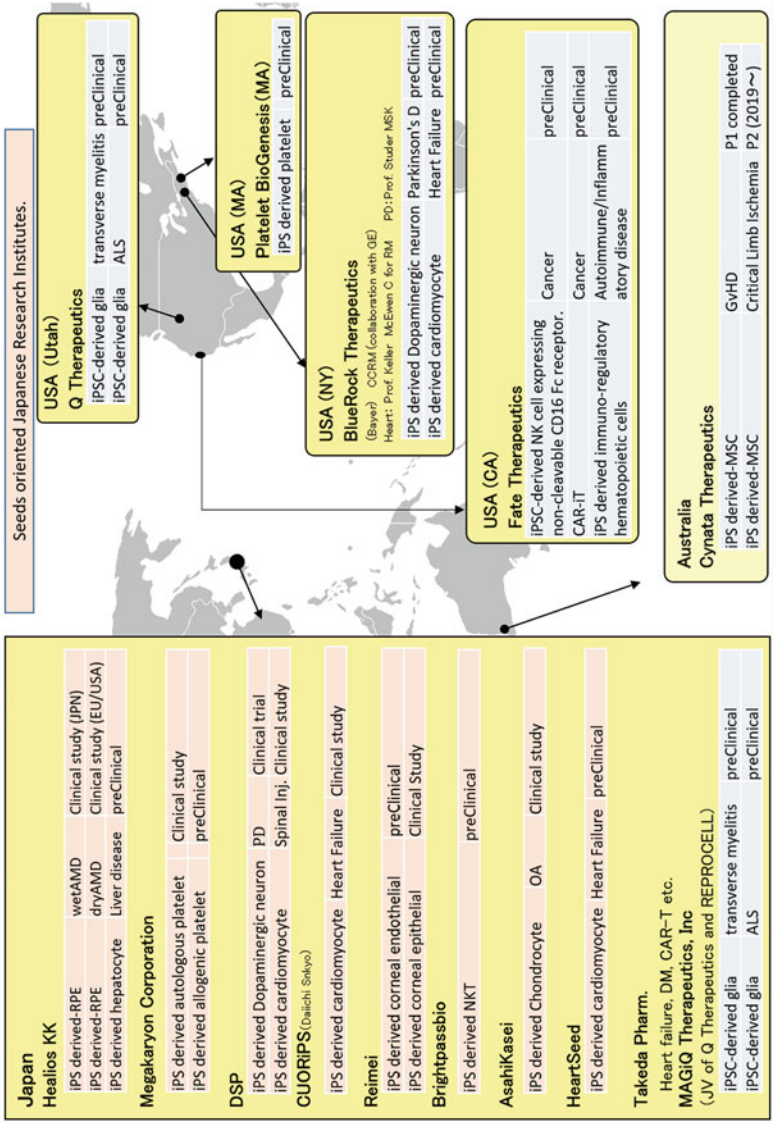
Seeds oriented Japanese Research Institutes.
Japan
Healios KK
iPS derived-RPE wetAMD Clinical study (JPN)
iPS derived-RPE dryAMD Clinical study (EU/USA)
iPS derived hepatocyte Liver disease preClinical
Megakaryon Corporation
iPS derived autologous platelet Clinical study
iPS derived allogenic platelet preClinical
DSP
iPS derived Dopaminergic neuron PD Clinical trial
iPS derived cardiomyocyte Spinal Inj. Clinical study
CUORiPS(Daiichi Snkyo)
iPS derived cardiomyocyte Heart Failure Clinical study
Reimei
iPS derived corneal endothelial preClinical
iPS derived corneal epithelial Clinical Study
Brightpassbio
iPS derived NKT preClinical
AsahiKasei
iPS derived Chondrocyte OA Clinical study
HeartSeed
iPS derived cardiomyocyte Heart Failure preClinical
Takeda Pharm.
Heart failure, DM, CAR-T etc.
MAGiQ Therapeutics, Inc
(JV of Q Therapeutics and REPROCELL)
iPSC-derived glia transverse myelitis preClinical
iPSC-derived glia ALS preClinical
USA (Utah)
Q Therapeutics
iPSC-derived glia transverse myelitis preClinical
iPSC-derived glia ALS preClinical
USA (MA)
Platelet BioGenesis (MA)
iPS derived platelet preClinical
USA (NY)
BlueRock Therapeutics
(Bayer) CCRM (collaboration with GE)
Heart: Prof. Keller McEwen C for RM PD:Prof. Studer MSK
iPS derived Dopaminergic neuron Parkinson's D preClinical
iPS derived cardiomyocyte Heart Failure preClinical
USA (GA)
Fate Therapeutics
iPSC-derived NK cell expressing non-cleavable CD16 Fc receptor. Cancer preClinical
CAR-iT Cancer preClinical
iPS derived immuno-regulatory hematopoietic cells Autoimmune/Inflammatory disease preClinical
Australia
Cynata Therapeutics
iPS derived-MSC GvHD P1 completed
iPS derived-MSC Critical Limb Ischemia P2 (2019~)

Fig. 7.6 Enterprises for iPS-derived products and their pipelines

efficacy of these treatments have been reported. As somatic stem cells do not require differentiation induction by gene transfer, they are regarded as a useful source for use in regenerative medicine.

7.2 Genome Editing of Human iPS Cells: An Overview of the Regulatory Framework

7.2.1 Overview

In connection with the Regenerative Medicine Promotion Act (adopted in April 2013 and promulgated in May 2013),[16] both the Regenerative Medicine Safety Act[17] and the PMD Act, which is the revised Pharmaceutical Affairs Law, have been adopted; this new legal regime was promulgated in November 2013 and entered into force on November 25, 2014.[18] The Regenerative Medicine Safety Act was intended to integrate the techniques of regenerative medicine, as far as they were conventionally used in separate areas of clinical research and medical services outside the scope of the national health insurance scheme into a single regulatory framework. Regarding its scope of application, the act includes regenerative medicines provided as a component of clinical research or medical care (including uninsured medical services). The PMD Act extends to regenerative medicinal products as a new category in addition to conventional pharmaceutical products and medical devices. It establishes a conditional approval system with time-limited validity of approvals depending on the product's properties (system to accelerate an approval). It mandates informed consent procedures to explain potential risks to patients and thereby to obtain consent. The act also requires the preparation and keeping of documents related to post-marketing surveys, sales, and use as an effort to secure safety. In this section, the framework for regenerative medicine in Japan will be discussed. This topic is regulated under the Regenerative Medicine Safety Act and the PMD Act.

7.2.2 History of the Adoption of Three Regenerative Medicine-Related Acts

There is a high demand within the population for regenerative therapy that could be applied to untreatable diseases; however, it is unknown if unapproved cell therapies in private clinics could lead to serious adverse outcomes.[19] To meet the demand, the

[16] Regenerative Medicines Promotion Act. http://law.e-gov.go.jp/html/data/H25/H25HO013.html.
[17] Regenerative Medicine Safety Act. http://law.e-gov.go.jp/announce/H25HO085.html.
[18] Pharmaceutical and Medical Device Act. http://law.e-gov.go.jp/html/data/S35/S35HO145.html.
[19] Ikka et al. (2015).

Japanese government launched two initiatives that included "A five-year Medical Innovation Strategy" in June 2012 and "The Japan Recovery Strategy" in July 2012.[20] In response to these initiatives, the Minister of Health, Labour, and Welfare ordered the Health Sciences Council Scientific Technology Panel to create a Subcommittee for Promotion and Assurance of Safety of Regenerative Medicines on August 20, 2012. The first meeting of this expert committee was held in September 2012.[21] At the time, it was unclear whether the human stem cell clinical research guidance issued by the Ministry of Health, Labour, and Welfare was to be revised or if new legislation was to be enacted. The committee's work was to be completed by summer 2013. Upon the news that the Nobel Prize was awarded to Professor Shinya Yamanaka on October 8, 2012, members of the Diet (Parliament) from three political parties agreed on October 23 to submit the proposed Regenerative Medicine Promotion Act in the next ordinary Diet session, and they discussed the submission of separate laws for regenerative medicine in the ordinary Diet session for the fiscal year of 2013. These decisions eventually pushed on the discussions in the second meeting of the expert committee in November 2012 not only in regard to the aforementioned human stem cell clinical research guidance, but also as regards the course towards new legislation. The third meeting of the committee in December 2012 confirmed the legislative direction. Consequently, the report "Structuring the Framework for Securing the Safety and Promotion of Regenerative Medicine" was drafted and reviewed in the seventh round of discussions in April 2013. Based on the report, the proposed Regenerative Medicine Safety Act was submitted to the Diet in combination with the revision of the Pharmaceutical Affairs Law (PAL). The bills were unanimously passed by the Diet. The Regenerative Medicine Safety Act and the PMD Act (i.e. the revised PAL) were adopted and promulgated on the same day, which can be translated into an implicit message indicating that the regulatory framework for regenerative medicine will be based on these two legislative paths for some time.

7.2.3 The Regenerative Medicine Promotion Act

The Regenerative Medicine Promotion Act was submitted to the Diet as a bipartisan lawmaker-initiated bill, and the legislation was then approved. The aim of the legislation is to ensure that the public is provided with access to regenerative medicine in a safe manner. This was enabled by the establishment of the basic concepts for promoting regenerative medicine research and development, supply, and distribution and by identifying the responsibilities of the Japanese government, medical practitioners, researchers, and business entities. This facilitated the comprehensive promotion of measures, from research and development to the

[20] Cabinet Office of Japan (2012).

[21] Prime Minister's Office of Japan (2012).

commercialization of regenerative medicine, thereby contributing to the improvement of the quality of medical services available for public health and hygiene. In regard to the responsibilities to promote regenerative medicine, the Japanese government is required to develop and implement comprehensive measures, provide education to the public, establish relevant ministerial collaborative structures, and announce basic directions of research and development and regarding the promotion of safe supply and distribution of regenerative medicines. Medical practitioners and researchers are required to cooperate with measures implemented by the Japanese government, while business entities are expected to collaborate with such governmental initiatives.

The following tasks are expected to be implemented by the Japanese government:

1. Legislative measures.
2. Promoting research and development of innovative regenerative medicine.
3. Coordination of the regenerative medicine environment.
4. Coordination of the clinical research environment.
5. Streamlining the structure for reviewing regenerative medicinal products.
6. Promotion of regenerative medicine business.
7. Securing human resources.

The establishment of the present legal framework is a historic milestone, as the Regenerative Medicine Safety Act was enacted to legally endorse regenerative cell therapy technology as medical practice provided in accordance with the Medical Practitioner Act/Medical Service Act. In the course of the PAL revision, a new chapter on regenerative medicinal products was included into the PMD Act (i.e. the revised PAL) with a view to regenerative/cell therapy.

7.2.4 The PMD Act (Revised PAL)

7.2.4.1 History

The adoption of the PMD Act (PAL revision of 2013, law pertaining to Ensuring Quality, Efficacy and Safety of Pharmaceutical Products, Medical Devices: Pharmaceutical and Medical Device Act) envisioned the taking of measures necessary to ensure the safe supply of pharmaceutical products and medical devices and to mandate for the first time the regulatory submission of package inserts, expanded the scope of certifications issued by registered notified bodies for medical devices, and established a system for conditional and time-limited approvals for regenerative medicinal products and other products. These implementing measures were to be laid down in a cabinet order within the prescribed time frames not exceeding 1 year after the promulgation of the revision which entered into force on November 25, 2014.

7.2.4.2 Overview of the PMD Act

Conventionally, pharmaceutical products that are to be manufactured and marketed are subject to regulations in regard to the commercial manufacturing and marketing of such products. In contrast, the PMD Act was initially intended to continuously and repeatedly regulate licenses for the manufacturing/marketing of pharmaceutical products by business entities in order to ensure the fulfilment of three requirements (efficacy, safety, and quality). For the purposes of adaption to changes of socioeconomic situations such as international consistency of the regulatory system, the development of scientific technology, and diversified corporate activities, the major revision in 2002 enhanced post-marketing safety measures and transformed the license approval system to a wholesale distribution system by ensuring that ensuring of safety of the distributed products is the essential component. This indicates that regulations were tightened to ensure the safe and effective use of products, and more focus was placed on follow-up regarding the distribution of products and any post-market adverse drug (side) effects.

Particularly in the case of regenerative medicines, a new definition was set up for regenerative medicinal products. In addition, new regulations/systems were established based on the properties and specificities of regenerative medicinal products. These new regulations/systems formed the outcome of discussions that identified the importance of achieving safety and reassurance by securing safety and ethics in regard to the properties of regenerative medicines which distinguish them from conventional pharmaceutical products/medical devices. This allowed for the implementation of measures for the smooth promotion of accelerated commercialization in response to the development of regenerative medicine research. Regenerative medicinal products include not only cell preparations and *ex vivo* gene therapy, but also *in vivo* gene therapies. These are different from the products covered by the Regenerative Medicine Safety Act which will be described later in this contribution. To easily capture the range of regenerative medicinal products covered by the PMD Act in comparison with the corresponding US and EU regulations, the range equates almost to "biologics" governed by the Center for Biologics Evaluation and Research (CBER) in the US; however, the category of "biologics" excludes protein drug products, therapeutic antibodies, nucleic acid medicine, and *in vivo* gene therapy. The range that is covered does include what are so-called ATMP (Advanced Therapy Medicinal Products) within the meaning of EU law.

It is noteworthy that the new act permits expedited, conditional, and time-limited marketing approval as an exception for inhomogeneous regenerative medicinal products when efficacy is anticipated and safety is demonstrated.[22] Although an exceptionally expedited conditional approval system was already stipulated in the previous PAL, the new law now clearly stipulates such an approval system to be applicable to the new category of regenerative medicinal products. Ambiguity remains as to whether non-homogenous regenerative medicinal products include

[22] Kuroiwa (2018).

autologous cell preparations or if regenerative medicinal products should be categorized as non-homogenous. Moreover, controversy remains as to the best method to predict efficacy and how efficacy should be interpreted. Additionally, whether efficacy may be assumed if some verified effective response is reported among many patients also remains unresolved. Currently, no Q&A notice has been issued in an effort to clarify these varying interpretations, thus ruling out the possibility that future regulatory reviews may delineate the interpretations of the law. Exceptional early approvals will involve verification of efficacy and safety as an effort for post-approval activities. If post-approval efficacy/safety evaluations are equivalent to re-examination, such as when pharmaceutical products may fail to demonstrate the predicted benefits, the exceptionally expedited approval will be revoked.

Under pharmaceutical regulation, pharmaceutical products/medical devices will receive regulatory approval if they meet the required quality/efficacy/safety standards in accordance with the state of science and technology at the time of clinical trial notification, clinical study, and approval application. The products/devices will be listed at national health insurance drug price or reimbursement price. Subsequently, the products/devices will be marketed in accordance with the health insurance law.

In general, pharmaceutical products/medical devices are commercialized following the steps of clinical trial notification, clinical studies, and ultimately, applications for regulatory approval. The safety and quality of the products for which an application for approval is submitted need to be demonstrated by meeting the standards for basic document preparation. Specifically, they must meet the requirements of a Ministerial Notification No. 1314 issued by the Pharmaceutical and Food Safety Bureau (PFSB) of the Ministry of Health, Labour and Welfare (MHLW) in 2000—Attachments 1 and 2 revision notices (five guidelines issued in 2012). Attachment 1 of the Notification No. 1314 is regarded as equivalent to the current Good Tissue Practice (cGTP) that specifies the concept of public hygiene to prevent the spread of transmitted diseases mediated by cellular tissue-based pharmaceutical products. The five guidelines issued in 2012 are intended to prevent undesirable changes/denaturalization of shapes/quality during the manufacturing process of regenerative medicinal products and thereby secure the quality/efficacy/safety of pharmaceutical products and medical devices.

According to the PMD Act, the manufacturing of regenerative medicinal products is required to observe the GCTP (Good Gene, Cellular, and Tissue-based Manufacturing Practice),[23] which is an original Japanese GXP, and not the GMP. The introduction of this practice reflects the fact that sterilization is not possible as in the case of low-molecular pharmaceutical products, and the view that manufacturing control for regenerative medicines requires careful management. It is noteworthy that a risk management plan for quality control was incorporated as a means for assessment and control in accordance with appropriate procedures regarding product

[23] Good Gene, Cellular, and Tissue-based Manufacturing Practice. https://www.pmda.go.jp/english/review-services/gmp-qms-gctp/0003.html.

quality risks over the entire duration from the early stage of development to the completion of the manufacturing process and marketing, ultimately allowing for the promotion of continuous improvements in product manufacturing procedures and product quality.

7.2.4.3 Regulatory Scientific Strategic Consultation

Ideally, regulatory scientific strategic consultation should be carried out prior to regulatory approval of regenerative medicinal products. The current regulatory scientific strategic consultation was adopted from the confirmatory application system initiated in 1999. Regulatory scientific strategic consultations should occur at the start of clinical studies, preferably in the order of consultations on quality, non-clinical safety, and clinical study protocols. Quality consultation verifies that the manufacturing and formulation process and the raw materials do not contravene the relevant regulations. After that, quality variables will be determined in an official consultation meeting. It is absolutely essential that the use of raw material must involve the conformity with the standards for raw materials and the verification of the entire tissues. Currently, many biospecimens that are to be used in regenerative medicine research must be demonstrated to comply with the standards for raw materials, although most of the cases fall short of achieving conformity with the raw material standards. In contrast, non-clinical safety consultation involves discussion of the entire tissues, as disclosure becomes unavoidable at that stage. Quality variables should be determined in regard to three aspects, i.e. the identification, efficacy, and safety of the cells used in the final drug products. Cell surface markers may be useful for identification of the cells, as other parameters may fall short of providing rational persuasion in terms of efficacy and safety variables. After quality consultation, the non-clinical safety consultation will discuss if first-in-man use is reasonably feasible. It should be noted that unless the manufacturing formulation process and quality variables are fully established, all of the studies may have to be repeated. Study repetition is warranted when even a slight variation in the manufacturing and formulation process no longer assures equivalence to the properties of the cells previously validated for safety. Furthermore, any changes to quality variables do not provide any safety assurance of quality comparability. Non-clinical safety consultations may discuss residual toxicities of low-molecular weight compounds used for inducing differentiation.

Clinical study protocol consultations will involve discussions on protocol and design decisions in an effort to validate the safety or efficacy based on non-clinical trial results. In particular target disease and subject inclusion criteria may be decided on the basis of a non-clinical efficacy study (non-clinical Proof-of-Concept (POC) study), while subject exclusion criteria will be decided on the basis of non-clinical safety study results. Some of the issues that require particular focus in non-clinical POC studies include the appropriateness of model animals, disease extrapolation to humans, and links among the variables in the model animals and those in clinical studies that are defined as endpoints. Insufficient non-clinical POC study designs

would undermine the possibility of proceeding to a clinical study. Still, clinical use can become possible even without POC in accordance with the Regenerative Medicine Safety Act. In such cases, the development stage will move to advanced medical care instead of a clinical study. In this case, an advanced medical care assessment panel will decide if these products can be covered by insurance for medical services.

7.2.5 Regenerative Medicine Safety Act

7.2.5.1 History

In relation to the enactment of the Regenerative Medicine Promotion Act, the Regenerative Medicine Safety Act was adopted as part of the duty of the Japanese government to promote legislation on regenerative medicines. This law is intended to clarify the measures related to the consideration of safety and bioethics in regard to the techniques to be used in regenerative medicines and other measures to be taken by the suppliers of regenerative medicines, to define the system related to manufacturing licenses for specified cell processing products in order to facilitate the expeditious supply and distribution of regenerative medicines, and to contribute to the improvement of medical services and health care quality (Article 1). The distinction from the PMD Act is that the products governed by the Regenerative Medicine Promotion Act are treated as part of medical technology provided under the Medical Practitioner Act/Medical Service Law, thus avoiding overlap with the PMD Act. The idea that the law can be traced back to the essence of the Directives for Human Stem Cell-based Clinical Research as former regulatory measures may facilitate a better understanding of the law. Consequently, the directives were abolished in connection with the enactment of the present law. A portion of the background to the adoption of the present law also relates to a fatality caused by a South Korean biotech company, RNL Bio, in Japan.[24] The fact that the term regenerative medicine is also used in the field of plastic surgery necessitated the registration of all medical institutions engaged in providing regenerative medicines.

This section will briefly discuss the history of the Regenerative Medicine Safety Act that resumed the regulatory intent of its predecessor, the Directives for Human Stem Cell-based Clinical Research. The directives were first formulated and issued as a regulatory guidance pertaining to regenerative medicine under MHLW Notification No. 425 in 2006. The directives were entirely revised by another Ministerial Notification (No. 380) in 2010 that took into account iPS cell-based regenerative medicine research. In 2013, the conditional use of ES cell-based regenerative medicine was permitted by Ministerial Notification No. 317. Originally, the principal investigators were required to wait for the review of their clinical research

[24] Ikka et al. (2015).

protocols by ethical and other committees established within their research organizations and for approval by the head of the research organization. They were then required to seek ministerial advice based on the Directives for Human Stem Cell-based Clinical Research before launching their regenerative medicine-based clinical research. At this stage, such practices were deemed special medical care which contravened Article 18 of the regulations on insurance medical institutes and long-term health care and were outside the scope of insurance reimbursement including the costs of covered general medical practices. The reason for these rules was that, even if explanations are provided to the patients and their consent is obtained, a difference in terms of understanding between the medical practitioners and their patients is likely to exist. Patients should not bear any unfair burden resulting from such difference, and any medical practices not validated for efficacy/safety should be avoided.

7.2.5.2 Overview of the Regenerative Medicine Safety Act

The Regenerative Medicine Safety Act contains two major cornerstones, i.e., on the one hand, mandatory adherence to the Regenerative Medicine Supply Standard (an ordinance) and adoption of penal laws for failure to adhere to ministerial orders such as suspension/improvement orders, and, on the other hand, involvement of a regenerative medicine committee within the framework of a prior review system. The regenerative medicine supply standards are specified in Article 3 of this act. Specifically, the supply must adhere to ordinances in accordance with Articles 42 and 44 (i.e. Articles 42 and 44 of said standards). Moreover, Article 3 of the act provides classifications of regenerative medicines into three categories that include Types 1–3 of regenerative medicines. These categories are based on the level of impact on human life and health. To facilitate the understanding of these classifications, Type 1 regenerative medicines represent a class of products derived from homologous cells and pluripotent stem cells or similar cells, while Type 3 regenerative medicines cover products intended for cancer immune therapy and those involving minimal manipulations such as platelet rich plasmas. This concept is illustrated as a flowchart that is available as Q&A notice (Fig. 7.7).

In the discussions during the legislative process, the categorization scheme was reviewed for its scientific rationality/ethics and was understood as a risk classification concept for the purpose of risk control. Specifically, Type 1 which includes iPS cell-based regenerative medicines (research) might involve unpredictable risks that require a sufficient level of discussion and thus require centralized review. Type 2 products are those for which risks have been identified as challenges in light of experiences from human stem cell clinical research directive reviews and, thus, review by a Specifically Certified Regenerative Medicine Review Committee will suffice. The Type 3 category merely requires discussion by the Certified Regenerative Medicine Review Committee, an internal ethics committee within a given organization, due to a non-significant risk level (Fig. 7.8).

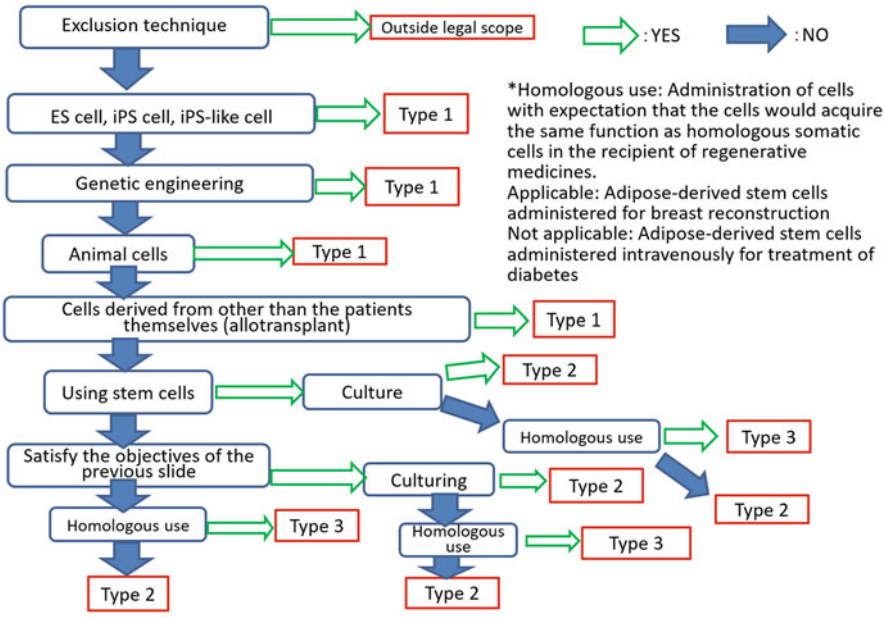

Fig. 7.7 Classification of regenerative medicines under the Regenerative Medicine Safety Act

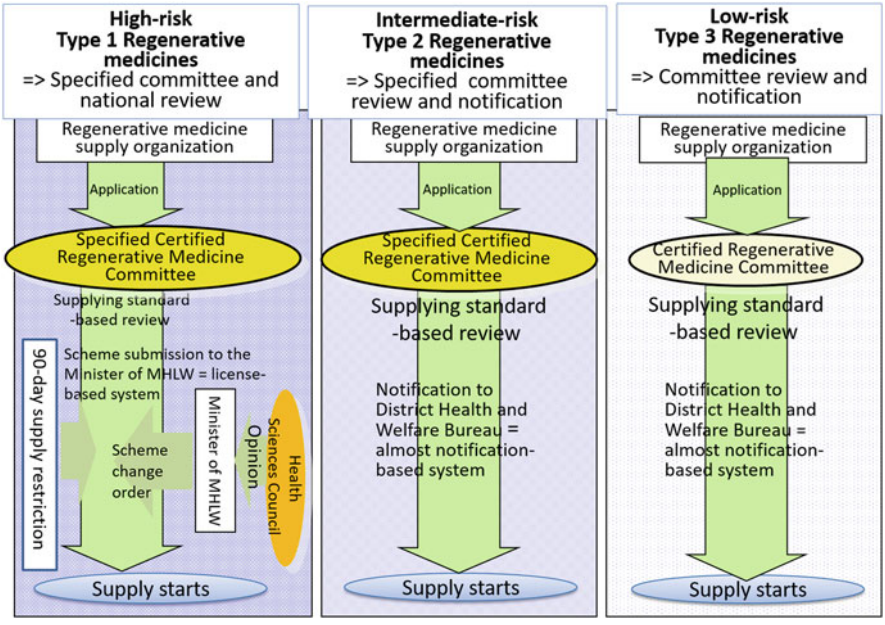

Fig. 7.8 Review framework for regenerative medicine in the Regenerative Medicine Safety Act

The supply scheme for Type 1 products is based on review by a Specially Certified Regenerative Medicines Committee (Ethical Review Board) and, thereafter, notification in writing to the MHLW Minister. This scheme involves a 90-day waiting period, during which the Health Minister seeks the opinion of the Health Sciences Council which has to verify safety. If the product fails to meet the safety standards, the Minister is empowered to order a scheme change. Several noteworthy points include (1) review by a specially certified regenerative medicines committee, (2) submission of a regenerative medicines supply scheme to the Health Minister, and (3) beginning of supply only after expiry of a 90-day waiting period (allowing for centralized review by the Health Sciences Council Regenerative Medicines Review Panel). These aspects are not substantially different from those related to review required under the former Directives for Human Stem Cell-based Clinical Research. The supply of Type 1 products is effectively subject to a permission-based scheme. The supply scheme of Type 2 regenerative medicines involves seeking the opinion of the Specially Certified Regenerative Medicines Committee and subsequent submission of reports in writing to the MHLW Minister on the product supply. The Type 2 scheme enshrines the aforementioned points (1) and (2) only and, thus, facilitates the double-layer review of Type 1 products, allowing this scheme to be classified effectively as a notification-based scheme. It has turned out, however, that the quality assurance by the Specially Certified Regenerative Medicines Committee may pose a serious challenge, and it is, therefore, likely that inadequate committees will eventually cease to exist. The Type 3 product supply scheme requires seeking opinions from the Certified Regenerative Medicines Committee followed by submitting reports in writing to the MHLW Minister on such supply. The Certified Regenerative Medicines Committee can be established by an individual medical institution, and, consequently, the levels of review can vary. Whether appropriate reviews are performed may dictate the future of regenerative medicines. Especially, the Certified Regenerative Medicines Committees are defined as expert panels that possess highly competent review capability and independence. Thus, not all medical institutions are able to create such committees. The committee is managed in a manner similar to that of the Central Review Board and will be required to undertake remunerated reviews.

As regards measures that ensure the proper supply of regenerative medicines, means to allow for informed consent and privacy information protection are defined, and adverse events should be immediately reported to the MHLW Minister. The Minister should then seek opinions from the Health Sciences Council on necessary measures, taking into account that regenerative medicines are not fully established within the health care system. The MHLW Minister is empowered to issue an order for improvement of safety measures. If such an order is violated, the Minister can impose restrictions on the supply of regenerative medicines and enact temporary measures to suspend the supply of regenerative medicine, if warranted, in order to prevent the spread of damage for health care reasons. This new authority granted under the medical service law to interfere with the supply reflects a response to the fatalities that occurred due to conventional non-insurance medical treatment.

To manufacture cell preparations (defined as specified cell processing products in legal terms), Article 42 of the Regenerative Medicine Safety Act specifies that the structures and facilities of the cell culture processing sites must satisfy the standards defined by the relevant ministerial ordinance. The act clearly states that the standards of the structures and facilities for manufacturing are to be specified by ordinance ('Article 42 Standards'). Article 44 of the Regenerative Medicine Safety Act stipulates that the Health Minister can define in a ministerial ordinance the methods of manufacturing and quality control, conducting study inspections, storage and transport, and all other issues pertaining to specified cell processing products at cell culture processing sites. The operation of these sites and their products should adhere to these laws, and the relevant standards should be clearly defined by an ordinance ('Article 44 Standards'). These standards are almost equivalent to the standards stipulated in the former Directives on Human Stem Cell Clinical Research. Thus, the enforcement of the new law does not cause any additional burden on research organizations and medical institutions that conducted clinical research on human stem cells in compliance with the former directives. Meanwhile, as the costs of the equipment and maintenance of these cell processing sites are prohibitive, the Regenerative Medicine Safety Act allows the outsourcing of the manufacturing of specified cell processing products. This idea stemmed from the presumption that outsourcing to an external organization with manufacturing capabilities would provide patients with specified cell processing products of a more stable quality. The quality levels to be met by contract manufacturing organizations inevitably became highly demanding. Notably, in view of the new legal framework, the law subjects medical institutions to a notification system and also imposes a licensing system on contract manufacturing organizations. Furthermore, when a medical institution outsources the manufacturing of a specified cell processing product, the external manufacturer must be a licensee or a notified business. Regarding the licensing of the manufacturing site of a specified cell processing product, it is expected that discussions of consequences arising from the law in practice may dictate the method of review and the required level of such review. However, given that the Pharmaceutical Products Medical Device Agency (PMDA) would provide reviews, it should be presumed that the level required may be equivalent to the standard for manufacturing sites that is detailed in the PMD Act. Externally manufactured specified cell processing products must be administered by medical practitioners. Accordingly, all the responsibilities are attributed to the medical practitioners that administer these regenerative products as well as to the responsible managers of the respective medical institutions, indicating that unless a defect of such specified cell processing product is demonstrated, the practitioners who administer the product must bear full civil and criminal responsibility. Moreover, it is predictable that some corporate entities may suggest that medical practitioners at medical institutions undertaking the production of regenerative medicines avoid PMD Act restrictions. However, the PMD Act regulations apply to a system within which the manufacturing enterprises practically distribute their own products.

7.2.5.3 Advanced Medical Care As an Exit from the Regenerative Medicine Safety Act

Concerns exist that regenerative medicines may not become widely available to the general public as medical care via the medical service law/medical practitioner act tracks. On the other hand, some medical researchers are concerned that promoting regenerative medicines through the pharmaceutical (medical device) law tracks will be challenging. Against this background, discussions are essential to support the design and management of a system to connect the several tracks. This system, known as advanced medical care, should allow for a connection between the Regenerative Medicine Safety Act and the PMD Act.

Advanced medical care is a new system established in April 2008 that succeeded its predecessor, the advanced medical care evaluation system (which is an obsolete system today), in a manner that allowed for expanded verification of efficacy in clinical use and included advanced medical care within the evaluation system (Notification 0331021 by the head of the Secretary-General of Health Policy Bureau, MHLW dated March 31, 2009). The advanced medical care system initially excluded advanced medical technologies using unapproved or off-label pharmaceutical products/medical devices which were outside its scope. However, as long as medical technologies within the third category of advanced medical care using unapproved or off-label pharmaceutical products or medical devices can be positively recognized as advanced medical care and the data obtained meets the cGCP level, the system allows the use of data from unapproved or off-label pharmaceutical products/medical devices in application documents for clinical trial notifications. This system seeks to bridge the advanced medical care under regulations of the medical practitioner act track with the PMD Act track using data collection tools for evaluation. Meanwhile, the advanced medical care evaluation system is essentially designed to bridge developments under the PMD Act with findings from companies that apply medical technologies intended for orphan diseases. This frequently results in a deadlock, though. Moreover, discussions evolved over the hierarchies regarding the review within the advanced medical care evaluation system and within advanced medical care. Consequently, advanced medical care in the second and third categories was included into the Advanced Medical Care Act.

In view of the quality and safety assurance and relief efforts for side-effects/adverse drug reactions, the pharmaceutical (medical device) law track can offer some benefits to facilitate relief, while in view of the possibility of clinical protocol improvement, the use of the Regenerative Medicine Safety Act may deserve consideration based on the ability of this law to offer more freedom with ample discretion left to medical practitioners. Hence, the proactive use of this system may render medical services provided outside the PMD Act appropriately useful for society.

When clinical research is completed in accordance with the Regenerative Medicine Safety Act and researchers conclude that certain levels of satisfactory safety/efficacy are achieved, evaluations will be performed to determine if such therapy

protocols should be covered by the national health insurance reimbursement program to ensure effective supply of adequate medical services. Specifically, if such clinical research protocols for medical treatments are deemed evaluable and are reviewed by the MHLW Advanced Medical Care Evaluation Committee to decide whether certain levels of efficacy/safety are rationally achieved scientifically and should be recognized as advanced medical care, basic costs can be claimed under benefits for non-insurance mixed medical care service expenses such as hospital fees. These specified medical care coverage systems are established with the intent to respond to the sophistication of medical services that are associated with improved levels of life. They are also established to account for diversified values among the public and the astounding advancement of medical practices and techniques and to provide tools for the adjustment of, on the one hand, appropriate insurance benefits to ensure access to necessary medical services and, on the other hand, patient choice for access to appropriate medical services. The systems serve as tools to validate if the application of advanced technology by medical practitioners within their medical institution occurs in accordance with the Medical Practitioner Act and possesses scientific rationality to be considered commercial health insurance treatment. The hope is that all clinical research conducted in accordance with the Regenerative Medicine Safety Act will offer benefits to society at large.

7.2.5.4 Tumorigenicity-Related Genes

Studies examining gene mutations in stem cells are inadequate, and the possibility of tumorigenesis is still unclear. Against this backdrop, the Ministry of Health, Labour, and Welfare has established a research team termed “Research on the way to evaluate the safety of transplanted cells when conducting clinical research using iPS cells”. Discussions were held on the basic concept of safety assessment, and they specifically focused on tumorigenicity of cells that were derived from pluripotent stem cells. They were compiled as “Comment for reviewers of tumorigenicity evaluation of regenerative medicine using human pluripotent stem cells in the Committee for Specific Regenerative Medicine”. In this document, the basic concept regarding the safety evaluation centered on the tumorigenicity of cells derived from pluripotent stem cells was described. Another document, the “Points to note regarding detection of undifferentiated pluripotent stem cells/transformed cells, tumorigenicity test and genetic stability evaluation of human cell processed products” has been also issued. A certain consensus has also been reached in regard to tumorigenicity-related test methods.

7.2.5.5 Reasons for Reforming the Regulatory Framework in Japan

In previous attempts to allow for a wider distribution of regenerative medicines through amendments to pharmaceutical affairs regulations, the former PAL dealt with only two categories, pharmaceutical products and medical devices.

Regenerative medicines became the source of confusion for academia, as the products could not be sterilized and thus could not be handled as pharmaceutical products. On the other hand, these products did also not fully fit into the conventional regulatory contexts for pharmaceutical products. Academia had to face patients under such a regulatory system with gloomy uncertainties and no clear directions. The desire for a means to address these uncertainties led to the upgrading of former Directives for Human Stem Cell-based Clinical Research through the Regenerative Medicine Safety Act and the clear establishment of regenerative medicinal products as a new category in connection with the enactment of the PMD Act (revised PAL). With these revisions, two regulatory paths became available for societal contribution to regenerative medicines. Japan is the only country among the developed countries in which society can participate in these two regulatory paths, and social experiments involving regenerative medicines allow for large-scale societal contribution to this exciting arena. Either path can serve as an answer to the question as to how regenerative medicines should permeate society.

7.3 Regulatory Prerequisites for Combined Gene/Cell Therapy Using Genome-Edited Human iPS Cells to be Differentiated into Somatic Cells for Autologous Retransplantation

7.3.1 Regulatory Practice for Regenerative Cellular Products in the PMD Act

Once manufacturing protocols for cells are established using *in vitro* studies, the manufactured cells are candidates for cell-based medicinal products. In order to judge if the cell-based medicinal products that have been manufactured according to the established protocols may be valuable for further development for clinical practice, pre-clinical studies have to be conducted. To allow for compilation of a pre-clinical study package for cell-based medicinal products, the pre-clinical study package used for chemical compounds is useful. The requirements and contents of the pre-clinical studies are classified into toxicity studies (general toxicity studies and special toxicity studies), pharmacological studies (primary pharmacodynamics studies and safety pharmacological studies), pharmacokinetic studies, formulation studies, and others. Pre-clinical studies for the cell-based medicinal products are conducted to evaluate and classify the efficacy and safety of the candidates. Arguments exist regarding the selection of assessment parameters in toxicity, pharmacological, and pharmacokinetics studies for cell-based medicinal products, as it is well-known that cell-based medicinal products possess different properties compared to those of chemical compounds. Notwithstanding the arguments surrounding the parameters used in these studies, the relevant assessment issues seem to represent an acceptable minimum consensus, and other parameters may have to be added on a

case-by-case basis depending on the cell manufacturing processes. In anticipation of approval for use as cell-based medicinal products, the possible requirements should be discussed already in the development process of such products from the standpoint of regulatory science, with particular focus placed on the requirements in pre-clinical studies.

7.3.2 Quality Control

7.3.2.1 Overview

It is important to ensure quality, as quality can be evaluated prior to clinical studies, while clinical studies are the only way to evaluate efficacy and safety (with the exception of some safety parameters evaluated in nonclinical studies). Quality control is required for test articles or products to ensure quality in terms of subject (patient) protection already in the research and development phase (ethical appropriateness), and it is important to improve the quality of clinical studies and to allow for a reasonable evaluation of the findings in terms of collection of knowledge and data for approval application, manufacturing, and marketing.

7.3.2.2 Quality Assurance from the Clinical Phase of Development to Manufacturing and Marketing

We would like to present a strategy for quality assurance from the clinical (trial) phase of development to manufacturing and marketing in research and development of cellular and tissue-based products. The aims are to establish quality control and assurance in the course of the manufacturing of test articles and nonclinical studies depending on the phase and to enable research institutes, such as universities and venture companies, to conduct sponsor-initiated clinical trials.

In the development phase, the quality control of a product occurs naturally in the testing or investigational stage. Consistency is required for the quality throughout the development phase. The term consistency can be interpreted as the state allowing for the identification of any difference. Comparability with the commercial product is required in Phase III and during confirmatory trials in the late development phase. The term comparability can be interpreted as the state that scientifically shows no significant difference and can be determined as comparable. The reproducibility of results obtained in multiple clinical studies is an important consideration in the approval review. Particularly for approval of low-molecular pharmaceutical products, it is preferable to investigate efficacy in more than one randomized clinical trial, and it is necessary to demonstrate the stability and reproducibility of the results obtained in the trials. Some applications were authorized on the basis of only one investigator-initiated trial, but they represent the cases where product efficacy was previously confirmed in clinical trials overseas or as an indication expansion.

7.3.2.3 Change in Regulatory Attitudes Toward the Quality of Pharmaceutical Products

The ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) meeting in 2003 was epoch-making in terms of attitudes regarding quality. It provided a concept to develop an applicable and harmonized quality system for pharmaceutical products (elaboration of quality) throughout the product life cycle with an emphasis on approaches combining quality risk management and science. This system can be regarded as a paradigm shift towards science- and risk-based approaches. There are some changes in the ICH quality guidelines where the trend shifted from the development of guidelines for specific test methods and specifications, such as specific stability test conditions based on trilateral harmonization, towards the development of guidelines based on conceptual principles of attitudes and methodology without providing specific numerical standards.

In conformity with this trend, the Japanese Pharmaceutical Affairs Law (PAL) was revised (and renamed as PMD Act) in order to hallmark the new direction of quality assurance. The original PAL focused on quality control based on the establishment of appropriate specifications, but the PMD Act (revised PAL) requires the establishment of a proactive quality assurance system for all phases from development to manufacturing for continuous improvement and flexible quality assurance depending on the product life cycle. As a basic idea in GCTP for Investigational Drugs (revised in 2008), the GCP Ordinance is recommended to be utilized as a component of quality management for the product life cycle and requires flexible application of appropriate requirements in consideration of situations and risks, as these standards are applicable to the several important phases in pharmaceutical development.

7.3.2.4 Common Technical Document (CTD)

The Common Technical Document (CTD) is a composition of marketing approval application documents that were agreed upon by the ICH and provided to pharmaceutical companies. The purpose is to reduce the overlap of tasks. It provides only a format for the compilation of application documents rather than a standardization of descriptions regarding quality. Both the CTD “Module 2: Overall Quality Summary” and the CTD “Module 3: Quality contain information regarding quality. Other publications” detail the composition of Overall Quality Summary.

7.3.2.5 Points for Regulatory Assessment of Quality and Quality-Related Documents Required for Approval

During the period from application to approval, quality is assessed in two situations which are approval review and GCTP inspection. GCTP is an acronym for Good Gene, Cellular, and Tissue-based Products Manufacturing Practice. GCTP is a GXP that adapts GMP (good manufacturing practice) to cell therapy products and is a Japan-specific regulation; however, it is not significantly different from USA and European GCTP standards. The approval review includes a team review and a reliability inspection, while the GCTP inspection includes an on-site inspection at the manufacturing sites. The approval review focuses on CTD "Module 2: Overall Quality Summary" in the approval application form by reference to CTD Module 3. For purposes of the GCTP inspection, the product master formula, standard operating procedures, and others are reviewed along with on-site inspections.

7.3.2.6 Ensuring Quality of Cellular and Tissue-Based Products

7.3.2.6.1 Ensuring Quality

In ICH-Q6A, "Quality" is defined as "the suitability of either a drug substance or drug product for its intended use. This term includes such attributes such as identity, content, and purity of the material." Quality assurance at the time of approval in simple terms is a system [. . .] that allows for the manufacture of products with the same quality whoever, whenever, and wherever they are manufactured. Products with the same quality should be controlled and ensured by manufacturing methods and specifications for final products, and quality is primarily confirmed during an approval review. The terms "whoever, whenever, and wherever" require control with some restrictions and are mainly confirmed in GCTP inspections.

The GCTP approach is adopted to ensure quality. This is because applicable notifications, guidelines, and other documents specify the means to ensure quality based on the GCTP approach. For investigational products, GCTP for Clinical Investigational Products and the so-called "Five Guidelines" issued in 2012 describe the means by which to ensure quality and especially quality requirements for final products. These requirements are specified in the chapter on "Method of Controlling the Quality of Final Products" in the said Guidelines.

7.3.2.6.2 Quality Control Items for Final Products

The Notification[25] states that the necessary and appropriate specifications of intended cells shall be set and justified by reference to general quality control

[25] Notification No. 0907-01~05, issued on Sep 7th, 2012 by Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Japan.

items and tests, including the number of cells and survival rate, identification test, cell purity test, tests on cell-derived physiologically active substances other than those desired, tests on process-related impurities, testing for sterility and the presence of mycoplasma, endotoxin tests, biological activity tests, potency tests, and mechanical compatibility tests. The number of cells and the survival rate are discussed on the basis of preventing efficacy reduction due to low cell survival rate and of safety as dead cells tend to promote clot formation. Although the Notification states the "number of cells," if the product will be administered as a cell suspension, the concentration must be evaluated. This is because excessively concentrated cell suspensions may cause an increased risk of embolism, and it is a critical evaluation item to ensure the quality to support the safety and efficacy.

An identification test is used to identify the desired cells by defining the critical measures of the cell characteristics, including morphological features, biochemical indices, immunological indices, characteristic substances produced, and other appropriate genotype or phenotype features. As emphasized by the term "desired," the identification test makes no reference to contaminants as impurities. This differs from the purity test. This test is not sufficient to identify mesenchymal stem cells as the desired cell for a given specification, as the quality items must be confirmed to ensure safety and efficacy. Mesenchymal stem cells are spindle-shaped adherent cells and immunologically defined as positive for CD44, CD90, and CD105 and negative for CD45 and others. The lack of an MHC class II expression can be also used as the quality index. If the mesenchymal stem cell is expected to inhibit or improve hepatic fibrosis, the secretion of collagenases such as MMP can be used as the quality evaluation item. Indices to identify the cell itself (e.g. CD44 positive), indices expected for the safety (e.g. MHC class II negative), and indices expected for the efficacy (MMP expression) should be considered to establish the identification test.

For the cell purity test, the Notification states that the test items, test methods, and acceptance criteria should be set for cell purity, including the presence or absence of cells other than desired (undifferentiated cells, abnormally-proliferating cells, and transformed cells) and the presence or absence of contaminated cells by taking into account the origin of desired cells and tissue and the manufacturing process including culture condition, quality control of intermediates, and others. In particular for cell products derived from pluripotent stem cells, residual differentiation-defective pluripotent stem cells should be considered, and it is essential to set the evaluation method and specifications for the residual ratio. Unlike in the purity tests used for low-molecular compounds, it is difficult to identify all cells other than as desired, and the specifications have to be established by investigating the toxicity caused by cells other than those desired in nonclinical safety studies and by applying certain margins. Practically, safety should be confirmed in a toxicity study using a cell product of the highest impurity ratio at an excessive dose to show non-linearity by utilizing the worst cases obtained in nonclinical studies.

Tests examining cell-derived physiologically active substances other than the desired substances are the opposite of the evaluation of desired physiologically active substances in an identification test. The Notification states that the appropriate

acceptable limit test must be established if a cell-derived physiologically active substance other than the desired substance may obviously pose a potential risk of significant safety issues for patients depending on the amount of the substance in the product. We must more clearly interpret the term "may obviously have" stated in the Notification. Although these tests are required, depending on the cellular features, they may be unnecessary if no toxicity was observed in nonclinical studies.

For tests involving process-related impurities, the Notification states that based on the results from an evaluation of the impurity removal process and in-process control test, their presence must be ruled out or the acceptable amount of impurities must be established using appropriate tests for substances that include substances that are derived from raw materials or materials used in the manufacturing process such as non-cellular components, culture media components, materials, and reagents that may be present in the product as contaminants, residues, newly formed or decomposed substances, or others and are undesirable from the viewpoint of quality and safety. The Notification requires justifying the selection of substances to be tested and establishing of the specifications. It also requires evaluation of the any substances that are undesirable in regard to quality and safety. Therefore, it is not necessary to set quality specifications for the shipment of substances that are not considered undesirable from the viewpoint of quality and safety. Even if a pharmaceutical product or other material is used in a cell manufacturing process and may be present in the cellular product or even if the material remains entirely in the final product (without removal by washing), quality specifications may not be required, based on discussions, if the amount is less than the proposed clinical dose administered once. One example is a pharmaceutical product of a Rho Kinase (ROCK) inhibitor used in a manufacturing process.

Testing for sterility and the presence of mycoplasma and the endotoxin test are recommended in accordance with the Pharmacopoeia. If a test method is confirmed as comparable to the method specified in the Pharmacopoeia, this test can be used for quality control even if it is not specified in the Pharmacopoeia. In other words, it is not necessary to use the method specified in the Pharmacopoeia; however, such a method can be used without discussion and may result in a reduction in the review period.

The Notification states that the biological activity test, potency test, and mechanical compatibility test can be chosen on the basis of the properties of the cellular product. For example, if hepatocytes regenerated from embryonic stem cells will be administered to improve hypoalbuminemia, the extent of the production and secretion of albumin is suitable for the quality control item. If the efficacy of a human somatic stem cell-processed pharmaceutical product is obtained from a certain physiologically active substance secreted from the cells and tissues (e.g. insulin-secreting cell), the test items and specifications related to the physiologically active substance are suitable for the quality control item in a potency test. If mechanical strength is expected as a feature of the product, such as for regenerated chondrocyte tissue, this product requires specifications to determine the mechanical compatibility and durability for the application site. If such a product will be administered to weighted sites, more rigid quality control is required.

7.3.2.6.3 GCTP As an Essential Prerequisite for Quality

The GCTP are standards for manufacturing and quality control of cellular medicinal products. GCTP defines, *inter alia*, the responsibilities, handling, and operations of, or by, employees, raw materials, equipment, manufacturing, products, tests, documents, waste products, etc.

The three principles of GCTP are:

1. prevention of error to minimize human error,
2. prevention of contamination to prevent contamination and quality deterioration, and
3. quality assurance system to design a system that ensures high quality. This system must be implemented and recorded.

GCTP requires both hardware and software. The required hardware includes facilities, equipment, and instruments, and the software relates to documents, manufacturing, test methods, cleaning, organization, education, and training for a complete quality assurance system.

Setting rules refers to organization of the document architecture, including statements, standards, and procedures, and these rules function to allow for elaboration of quality by following a cycle that consists of defining rules (documentation), implementing the rules (recording), checking the rules (evaluation and discussion), and improving the rules (review of the rules).

In regard to elaboration of quality by following a cycle, this means a spiral improvement of quality that does not always require uniformity of GCTP control. If the GCTP for manufacturing is different, depending on the importance of development phase or process, preparing the Standard Operating Procedure (SOP) and filing the records is sufficient for Phase I studies. Preparing the SOP, evaluating the process, operation, and equipment, and confirming and filing the records are necessary for Phase II studies. Phase III requires preparing the SOP, implementing and recording the validation of the processes, operations, and records, and subsequent approval and filing by the Quality Assurance Section for comparability with the product after application approval. In any case, it is essential for GCTP control to prepare the procedures and file the records. An SOP is required for all operations. SOPs are also necessary for operations that do not regularly occur (e.g. handling of out-of-specification materials), and any operation not to be implemented (e.g. repeated measurement is not acceptable) must be clarified. It is essential for quality control not to change the operations without approval, and change control is required to improve or change the SOP. Deviation control is required for non-compliance with the SOP (deviation). Any improvement or change can be implemented by following the appropriate procedures. Thus, the procedures must be defined for change and deviation control. The elements required for the SOP must clearly describe the necessary operations as specified for the individual and for all operations, and these documents must be accessible and be frequently updated. The SOP document architecture should be constructed with these elements in mind.

7.3.2.6.4 GCTP in Cellular and Tissue-Based Products

There are two means for quality control, i.e. the review of the approval application and the evaluation of the GCTP. The latter is easy to understand by referencing Sections 1 and 2 in chapter 2 "Method of Manufacture" in the so-called "Five Guidelines" from 2012. Raw materials and manufacturer-related substances can be divided into desired cells and tissue and raw materials and manufacturer-related substances other than the desired cells and tissue. The former substances are consistently present from acceptance to shipment while the latter are added and washed. The GCTP acceptance control of raw materials is applicable.

For the desired cells and tissue, the origin and derivation, reasons for selection, characteristics, and eligibility of the desired cells and tissue as the starting material should be discussed and accompanied by bibliographic references based on the results of studies conducted by the applicant. In addition, the Notification[26] states that the characteristics of biological structures and functions should be indicated using appropriately chosen indices specific for the desired cells and tissue, and the reasons for selection of the cells and tissue as the raw material should be described. The starting cells and tissue themselves should be primarily considered to describe the origin and derivation, the reasons for selection, their characteristics, and the eligibility of the desired cells and tissue. Additionally, *ex vivo* cell properties of superiority in differentiation induction, activity after administration of the cellular product, and other properties should be primarily considered to describe the reasons for selection of the cells and tissue as the raw material.

For non-autologous cellular and tissue-based products, donor information must be compiled and filed to allow for access to necessary information to ensure safety of the desired cells and tissue. As the risk of transmission of infectious diseases must be reduced, it is necessary to refer to the GTP Notification.

For collection, preservation, and transportation of cells and tissue, the eligibility of collectors and collecting medical institutions is specified to avoid contamination of collected cells and tissue and to ensure the safety and privacy of donors. To clarify the technical requirements of collectors and collecting medical institutions with regard to the desired cells and tissue, it is necessary to demonstrate that the collector is a physician who is preferably well-trained and specialized in the applicable domain, and the collecting institutions are limited to medical institutions that have the facilities to reduce the contamination risk. Raw materials and manufacture-related substances other than the desired cells and tissue are, for example, culture media, cytokines, and feeder cells if appropriate. The Notification states that it is necessary to identify the raw materials and manufacturer-related substances other than the desired cells and tissue, to show eligibility, to set the specifications as needed, and to perform appropriate quality control. Setting of acceptance specifications and acceptance inspections will be conducted during the manufacturing

[26] Notification No. 0907-01~05, issued on Sep 7th, 2012 by Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Japan.

process. The manufacturers must comply with the related laws, regulations, and notifications, including the Standards for Raw Materials Originating from Living Organisms, regarding the use of any biological product or specified biological product as a raw material. As Notification No. 210 is based on Article 42 of the PAL (Pharmaceutical Affairs Law) it is also called the Standards of Article 42 of PAL one of them being the Minimum Requirements for Biological Products. If any material is not in compliance with the Standards, the product cannot acquire marketing approval. Sufficient consideration is required before beginning clinical studies.

The section detailing the Manufacturing Process contains the acceptance inspection, inactivation and removal of bacterial fungi and viruses, microcutting of tissue, separation of cells, isolation of a specific cell, preparation of cells as a component of the final product, establishment and use of cell lines, cell bank construction, and prevention of misidentification and cross-contamination during the manufacturing process. All of these correlate well with the GCTP quality control and should be described in the SOPs for control.

As the descriptions in the application form are approved, any deviation from the description is regarded as a violation of the PAA as far as specific control values or parameters, such as operation conditions, are described in the column for the manufacturing method. Therefore, attention is required to avoid any inconsistency between the application form and product master formula (GCTP). The application form should contain the necessary and selected operation procedures for the manufacturing process to ensure consistent quality, and thus, it should be considered to describe the target values and settings on the application form while describing the actual control range in the product master formula for control by the GCTP.

7.3.3 Pre-clinical Studies

7.3.3.1 Definition

Once protocols for cell-cultivation have been established using *in vitro* studies, the differentiated cells are assigned as candidates for cell-based medicinal products. To judge if the cell-based medicinal products manufactured according to the established protocols are valuable for further development for clinical practice, pre-clinical studies shall be conducted.[27]

The pre-clinical study package used for chemical compounds will aid in the construction of a pre-clinical study package for cell-based medicinal products, although it is well-established that the cell-based medicinal products possess properties that are different from those of the chemical compounds. Pre-clinical studies

[27] U.S. Food & Drug Administration, Guidance for Industry, Preclinical Assessment of Investigational Cellular and Gene Therapy Products (Nov. 2013). https://www.fda.gov/media/87564/download.

are classified into toxicity studies (general toxicity studies and special toxicity studies), pharmacological studies (primary pharmacodynamics studies and safety pharmacological studies), pharmacokinetic studies, formulation studies, and others. The pre-clinical studies are conducted to evaluate and qualify the efficacy and safety of the candidates for the cell-based medicinal products. Collection of available information to conduct clinical trials, such as those regarding selection of surrogate markers, is among the objectives of the pre-clinical studies. Once an unexpected adverse event occurs during the course of clinical trials, the pre-clinical studies should be reviewed to retrospectively identify its cause. Although all toxicological studies and some safety pharmacological studies must be conducted in compliance with the Good Laboratory Practice (GLP) Ordinance, not all of these studies are required to be completed under the GLP Ordinance until the start of the first-in-man trials.

7.3.3.2 Toxicity Studies

7.3.3.2.1 Objectives of Toxicity Studies

The primary objective of toxicity studies is to evaluate the safety of the candidates for cell-based medicinal products by identifying the types of toxicity and the tissues/organs where toxicity occurs. The toxicities of the cell-based medicinal products include the toxicity being an extension of their primary pharmacological actions, and toxicity associated with the properties of the products and their pharmacological activities. An example of the former is myocardial rupture associated with cell products for myocardial infarction due to effects on myocardial fibrous tissue resolution as its primary pharmacological effect, while an example of the latter is ossification after administration of the product to cardiac milieu, ultimately resulting in arrhythmia.[28] In general, the former events could be predictable, while the latter events are unpredictable and can possibly result in serious outcomes.

7.3.3.2.2 General Toxicity Studies and Cell-Based Medicinal Products

General toxicity studies are categorized into two types that include single-dose toxicity studies and repeated-dose studies.[29] These toxicity studies are mandatory for cell-based medicinal products, as they are required for the approval of a chemical compound as a new drug. Single-dose toxicity studies (acute toxicity studies) are conducted to determine the potential toxicity of the cell-based medicinal products after a single dose. For chemical compounds, a 14-day post-dose observation period is required, and necropsy including gross pathological and histopathological

[28] Wong (2011).

[29] Redfern (2015).

examination is performed when appropriate. For cell-based medicinal products, controversy remains as to whether toxicity studies should be conducted with the products per se or its analogue derived from the test animal species. The use of an analogue from the test animal species in toxicity studies is, in general, not appropriate, although it seems more rational than the use of human-derived products in immunodeficient/immunocompromised or immunosuppressed animals to assess the potential toxicity of the product itself.

Unlike chemical compounds, it is difficult to estimate the lethal dose of cell-based medicinal product in general toxicity studies. Originally, single-dose toxicity studies were designed to demonstrate the occurrence of toxicity due to accidental overdose and/or to determine doses for appropriate repeated-dose studies. In regenerative cell therapy, accidental overdose, for example 10 times or more of the standard dose, is highly unlikely to occur. Therefore, the toxicity is considered to be adequately evaluated with doses over the clinical dose up to the maximum dose technically possible. For this purpose, safety dose determining studies should initially be conducted to determine the maximum dose technically possible in conjunction with collection of the basic data on organ toxicity that should be reflected by single-dose toxicity studies conducted in compliance with the GLP. Repeated-dose toxicity studies (sub-acute and chronic toxicity studies) are designed to determine the potential toxicity of the cell-based medicinal products after repeated exposure. The purpose of these studies is to provide an observation for toxicity accumulation. Based on the results of the repeated-dose studies, the no observed adverse effect level (NOAEL) is estimated, and this is used for the planning of clinical trials. Many of the cell-based medicinal products do not require repeated-dose toxicity studies, as once the cells have survived following a single dose, long-term exposure is expected. Repeated-dose toxicity studies are required, however, for repeated-use products.

There is still a great deal of debate regarding the selection of toxicity assessment parameters for cell-based medicinal product. Besides parameters used in general toxicity studies, the assessment of tissue toxicity may be an assumable minimum consensus, and other assessment parameters should be added on a case-by-case basis depending on the cell manufacturing processes.

7.3.3.2.3 Special Toxicity Studies and Cell-Based Medicinal Products

Special toxicity studies that are required for low-molecular weight compounds include carcinogenicity studies, antigenicity studies, genotoxicity studies, reproductive and developmental toxicity studies, and, if appropriate, local tolerance studies, dependence studies, and photo toxicity studies.[30] Carcinogenicity studies of chemical compounds are to be conducted if (1) the results of genotoxicity studies suggest a concern regarding carcinogenic potential, (2) a possible risk of cancer in humans

[30] Marey et al. (2016); Mead (2014); Yan and Song (2014).

has previously been indicated, (3) the structure-activity relationship suggests genotoxic and/or carcinogenic potential, (4) repeated-dose toxicity studies provide evidence of paraneoplastic changes, and/or (5) the parent compound or its metabolite (s) remain in the tissue for an extended period of time, possibly resulting in local histological or pathological changes. Carcinogenicity studies are also required for chemical compounds intended to be used for at least 6 months.[31] The required observation period is 24–30 months for rats and 18–24 months for mice and hamsters. Antigenicity studies are intended to evaluate antigenic potential in guinea pigs that are challenged repeatedly with the test compound or a compound-protein conjugate, and this is followed by boosting for 2–3 weeks after challenge.

The issue remaining to be addressed for the implementation of carcinogenicity studies of cell-based medicinal products is how to evaluate possible malignant transformation of the cells themselves after administration. With respect to genotoxicity studies, the question of whether cell-based medicinal products can induce malignant transformation into tumor cells remains unanswered. There have been no reports of malignant transformation after transplantation in cases of mesenchymal stem cells or other somatic stem cells. In contrast, it has been reported that iPS cells transformed into tumor stem cells when co-cultured with tumor cells.[32] Consequently, more consideration will be needed for pluripotent stem cell (ES cells/iPS cells)-derived cell products. For reproductive and developmental toxicity studies, cell products do not appear to affect the reproductive glands and are highly unlikely to cause reproductive and developmental toxicity.

A tumorigenicity test will be mandatory for pluripotent stem cell (ES cells/iPS cells)-derived medicinal products, as these cell products were obtained from immortal ES cells/iPS cells. There is currently only one reference guideline (WHO-TRS978).[33] In the testing protocol (WHO-TRS978), test cells were transplanted into 10 nude mice (immunocompromised mice) at a dose of 1×107 cells/animal. The mice were, then, observed for subcutaneous tumor formation for 16 weeks. This guideline was originally developed for quality control for a master cell bank in the manufacturing of protein products and other biologics. The statement that this test should not be applied for cellular therapy products is included in an Appendix of the 2010 revised version of WHO-TRS878. Currently, there are no guidelines regarding tumorigenicity studies for cell-based medicinal products. Unlike with conventional chemical compounds, possible interactions with surrounding tissues and locally administered pluripotent stem cell-derived products should be considered. Therefore, in practice, the tumorigenicity studies might be performed in conjunction with a chronic toxicity study or a disposition study (metabolic fate study) to observe the consequences of interactions between the cell products and

[31] van der Laan et al. (2016).

[32] Sancho-Martinez et al. (2016).

[33] WHO Expert Committee on Biological Standardization (2013).

surrounding tissues and the potential toxicity of a locally formed tumor to organs or tissues (if formed).

7.3.3.2.4 Pluripotent Stem Cell Input Studies

We propose a pluripotent stem cell input study to evaluate the safety of iPSCs and other pluripotent stem cells-derived products. The studies should be performed to assess if un-/low-differentiated and/or differentiation-resistant ESCs/iPSCs are contaminated and if the contaminated cells could form teratomas *in situ*. To achieve this, a residue assay and detection system should initially be established using contaminated pluripotent stem cells in the product of interest. An amount of the undesired cells beyond the threshold of the system used is mixed with the cell products, and then teratoma formation is assessed after administration or transplantation. A residue assay and detection of differentiation-resistant pluripotent stem cells could utilize a nucleic acid amplification technique (NAT) (e.g., *Alu*-PCR technique) or flow cytometry as reported.[34] For example, if 0.01% residue is the threshold of detection according to a cold run, pluripotent stem cells are mixed at a concentration above 0.1%. It is ideal that pluripotent stem cells are mixed at a concentration 10 times the limit of detection to ensure non-linearity. Pluripotent stem cells themselves may be required to be administered or transplanted as a positive control. A cell-based medicinal product mixed with pluripotent stem cells would be transplanted to the intended site of transplantation in clinical practice, and then teratoma formation would be assessed. The animal species is selected on a case-by-case basis, depending on the route of administration and other factors. The required duration of observation, referred to in the carcinogenicity studies, may be 24–30 months for rats and 18–24 months for mice or hamsters. It may be recommended that all animals be observed until death to obtain a survival curve based on the assumption that tumor formation does not necessarily shorten the life span and that prognosis may be even improved as a result of improvement in the disease condition; however, this observation is time-consuming and some patients may miss the opportunity to receive a benefit from the cell-based medicinal product. Therefore, to assess tumorigenicity, animals should be sacrificed during the course of study at approximately 6–9 months after administration of the product mixed with pluripotent stem cells, and a first-in-man study will be warranted if there is no evidence of teratoma formation at this time point. The number of animals sacrificed in the course of the study and the duration of observation from dosing to sacrifice can be determined based on available evidence. For example, if no teratomas were formed from iPSC-based medicinal products for at least 6 months after transplantation, this finding could be the theoretical rationale for determination.

[34] Okura et al. (2011a).

7.3.3.3 Pharmacology Studies

7.3.3.3.1 Pharmacology Safety Studies

Pharmacology safety studies are used in combination with primary pharmacodynamics studies as the mainstream of pharmacology studies. Pharmacology safety studies, also known as general pharmacology studies, are meant to determine the potential undesired pharmacological effects of the cell-based medicinal product on physiological functions. Pharmacology safety studies consist of core battery, follow-up, and supplemental safety pharmacology studies, but some observations can be undertaken simultaneously.

The core battery is meant to investigate the unfavorable pharmacological effects of the product on the physiological functions of the vital organ systems such as the cardiovascular, respiratory, and central nervous systems (CNS). Cardiovascular parameters include blood pressure, heart rate, and electrocardiogram. Respiratory parameters include various respiratory function tests such as respiratory rate, tidal volume, and Hb oxygen saturation. CNS parameters include motor activity, behavioral changes, and body temperature. For individual cell-based medicinal products, specific parameters may be included depending on the mode and route of administration. For example, in the case of injection of cell suspension into the coronary artery, cardiac output and ventricular contraction (wall mobility) should be additional parameters, as the injected cells may cause microinfarction. For a cellular product injected into a vein for the treatment of cerebrovascular disorders, observations of blood pH and LDH levels are recommended, as the injected cells may cause pulmonary embolisms that result in infarction. Behavioral pharmacology, learning, and memory should also be assessed, as the product is intended to treat cerebral infarction. These additional observations are referred to as follow-up studies and should be undertaken if further investigation is considered necessary based on the results of the core battery. Follow-up studies should be conducted in compliance with the GLP Ordinance to the greatest extent feasible, but they are not required to be fully GLP compliant. It is recommended that a follow-up study be included in the core battery to be conducted as a combined study, as some effects related to the testing of cellular product that would be observed in the core battery can be expected. Supplementary pharmacology safety studies are meant to evaluate potential adverse pharmacodynamics effects on organ system functions that were not addressed by the core battery or repeated dose toxicity studies when there is a cause for concern.

7.3.3.3.2 Primary Pharmacodynamics Studies

Primary pharmacodynamics studies are intended to support the effects of a test cell-based product in relation to its desired therapeutic target. The study method varies depending on the effects and indication. These studies are conducted to support pharmacological effects not only in *in vivo* studies but also in *in vitro* studies.

Pathophysiological animal models are often used in primary pharmacodynamics studies, while healthy animals are used in general toxicity and safety pharmacology studies. It may seem that primary pharmacodynamics studies are essentially the same as primary pharmacodynamics studies conducted in many non-pharmaceutical laboratories. Such studies that are commonly performed by many non-pharmaceutical researchers may be considered as primary pharmacodynamics studies if their reliability is sufficiently assured for new drug applications. It is important to investigate the mechanism of action of the test product as a key factor in determining endpoints or surrogate markers/parameters in clinical trials. Additionally, a dose-range finding study to evaluate the efficacy of the test product is required to prevent an excessively high exposure in subjects and patients. A dose-range finding study to evaluate efficacy includes 4 dose groups given either the test product at 1/3 and 3 times the anticipated optimal dose or the vehicle only, and the study ensures the linearity of the dose-response relationship within the dose range used. In general, 5 or more measurements are required to ensure the reliability of the standard deviation, although at least 3 measurements are needed to calculate the standard deviation. Thus, primary pharmacodynamics studies include 5 animals, assuming that some deaths may occur in the course of the study. It can be assumed that linearity (continuity) is maintained in the dose range from more than 1/5 to less than 5 times the anticipated optimal dose. Dose-range finding studies to evaluate the potential toxicity after a single dose include a dose level of more than 10 times the effective dose to ensure nonlinearity (discontinuity), and further development is warranted if no toxicity has been observed in rodents at these dose levels.

It is important to determine which rodents or non-rodents are included, what kind of pathophysiological animal model should be used, and what parameters should be assessed. For example, in the case of a cell-based medicinal product that is injected into the coronary artery for the treatment of a cardiac disorder, it is difficult to make proper assessments in rodents due to their vascular size. Cardiac function can be evaluated in large animals such as swine by CT, MRI, or echocardiography. It is also important to elucidate the mechanism of action in primary pharmacodynamics studies. Pluripotent stem cell-derived cardiomyocytes must be observed for their survival and maturity to myocardium after transplantation to the myocardium. In contrast, if the proposed pharmacological effect is a cytokine effect, angiogenesis or activation of endogenous stem cells in cardiac milieu should be evaluated. If fibrinolytic effect is the key pharmacological outcome, then a comparison of the percentage of the fibrosis area ratio on histological specimens stained with Masson trichrome and Sirius red or other specific parameters is needed. The results obtained from these pre-clinical studies are also important in terms of intellectual property. In the extrapolation of the results of pre-clinical studies to a first-in-man clinical trial, the continuity of endpoints, surrogate markers, and parameters should be taken into consideration.

7.3.3.4 Pharmacokinetic Studies/Disposition Studies

Pharmacokinetic studies of chemical compounds are intended to evaluate the absorption, distribution, metabolism, and excretion (toxicokinetic studies) of the compound, and they are collectively referred to as ADME (T) studies. The results of pharmacokinetic studies are used in combination with those of toxicity and pharmacological studies for the planning of clinical studies. Pharmacokinetic studies are not required to be GLP compliant; however, they should be conducted in accordance with reliability standard requirements.

Disposition or metabolic fate studies, but not pharmacokinetic studies, are required for drug products of cell-based medicinal products. Disposition studies determine the distribution of a cellular product in organs facilitated by the intended mode of administration or transplantation, and they are conducted to observe potential organ toxicity if the cell products locate to undesired organs. The timing of the post-dose observation period is controversial, but logic may be constructed on a case-by-case basis depending on the properties of the cell-based product. For example, a 3-month post-dose observation period may be applied to a cellular product with cytokine effect, as the cells are not expected to survive for a long period of time. In contrast, a 6-month or more post-dose observation period may be necessary for cardiomyocytes derived from pluripotent stem cells, as these are anticipated to survive and have an effect in the cardiac tissues as replacement therapies.

A major issue is the tracking of administered cells. To date, cells have been labelled with Indium-111 or other radioisotopes, and the distribution of radioactivity in the organs has been considered to be that of the administered cells. The radioisotope method does, however, possess limitations. First, it does not always track only viable cells after administration, and second, the half-life is too short to be used for long-term tracking. Disposition studies of human-derived cells can include cell tracking using immunohistochemical detection with an anti-HLA antibody or using an *in situ* FISH technique. We have reported an *Alu*-PCR detection method based on the *Alu* sequence, a repetitive sequence specific to humans.[35] Another issue is which organs should be observed in a disposition study. Observation of only organs with high blood flow (such as the heart, liver, kidney, and brain) is insufficient, although the organs to be observed depend on the route of administration. We have proposed a list of more than 30 organs to be assessed based on the organ panel that is used in marketing applications of an antibody drug.[36] We also reported procedures for the findings of abnormalities such as mass formation on gross pathological examination and histological examination.[37] For mesenchymal stem cells, it is necessary to examine possible ectopic differentiation to bone, cartilage, and fat as assessed by histological examinations using staining with von Kossa,

[35] Saga et al. (2011).
[36] Okumura et al. (2016).
[37] Okura et al. (2011b).

Alucian blue, and HE, respectively. In the case of ESCs/iPSCs-derived products, immunohistological examination may be included for the detection of residual un-/low-differentiated pluripotent stem cells.

7.3.4 Case Study

In this section, a case study will be presented that includes allogenic iPSC-derived T cells for CAR-T with HLA-knockdown as an example of regenerative medicinal products. To secure the safety of the regenerative medicinal product, a risk based approach indicates three major issues. The first issue is the risk of transmittable infectious diseases, which is a hygiene risk. The second issue is the hazard that the specifications of the cells could be unintentionally altered by genome editing and/or modification. The last issue is the hazard that gene introduction could result in genes or their fragments inserted into the genome, ultimately resulting in tumorigenicity.

Prior to the manufacturing process, biospecimens should be procured form donors. To avoid carryover of the transmitted disease, the eligibility of the donors should be examined under GTP (Good Tissue Practice). The Medical Practitioners Act requires doctors to procure the biospecimens in clinics or hospitals.

Subsequently, the biospecimens should be sent to the manufacturing center. Only T lymphocyte-derived iPS cells could differentiate into iPS cell-derived T lymphocytes, and therefore, T lymphocytes should be collected from peripheral blood and cultured to outgrowth. Materials, activating-antibody, culture media, and cytokines should be selected to avoid the transmission of diseases from human materials and/or non-human animal-derived materials.

Then, the culture peripheral T lymphocytes derived from healthy donors should be treated with reprogramming factors. According to the applicable regulations, the regulators speculate if retroviral or lentiviral introduction of the reprogramming factors would deliver structural abnormalities to the genome, and the manufacturers are instructed to avoid the use of these transduction technologies. Against this backdrop, an episomal non-integratable transduction system has been used in CiRA, Kyoto University, in which the HLA homologous iPS cell stock has been established.

After establishing the T lymphocyte-derived iPS cells, we move to the next step that involves HLA-knockdown/out where genome editing technologies should be applied. Using CRISPR/Cas9 and other techniques, the HLA locus of the genome of iPS cells would be knocked down/out. There are three major issues, including on-targeted or non-targeted mosaicism of CRISPR/Cas9 and other treated iPS cell populations, off-target effects on the genomes of the treated cells, and on-target insertion/deletion abnormalities within the genomic structure. To avoid mosaicism, single cells should be isolated form the CRISPR/Cas9 and other technique-treated iPS cells, re-cultured, and expanded. Single colony-derived iPS cells should be examined in regard to their genome to obtain the intended HLA-knockdown/out iPS cell lines.

In the next step, a number of lines derived from the single colony-derived iPS cells should be sequenced in regard to their genome to avoid on-target insertion/deletion abnormalities and off-target effects on the genomic structure. To sequence the genomes, there are three approaches that include whole genome sequencing (WGS), whole exome sequencing (WES), or direct sequencing of the genes listed. The on-target insertion/deletion abnormalities within the genomic structure may be detected by direct sequencing of the intended target genes and their neighbors. The off-target effects on the genomic structure could not be predicted exactly, and therefore, CiRA (Kyoto University) decided that WGS techniques should be applied for genome edited iPS cells in the respective iPS cell bank. There is no list of genes that should be examined. Against this background, we proposed the cancer related gene list, Cosmic Census, and the Shibata list, which possess 700 genes. As of 2019, the list is under revision by the Ministry of Health, Labour, and Welfare of the Japanese government.

The HLA-knockdown/out iPS cells should be expanded and differentiated into T lymphocytes. After initiation of this manufacturing process, this process should be regulated by GCTP under the PMD Act to produce market available products in accordance with approved protocols under the Regenerative Medicine Safety Act. Materials, activating-antibody, culture media, and/or cytokines should be selected to avoid the transmission of diseases from human materials and/or non-human animal-derived materials in all manufacturing processes.

To manufacture CAR-iPS-derived T cells, the expanded iPS cell-T lymphocytes should be exposed to CAR vectors. After transduction of CAR vectors, the integrated sites should be examined. In the Common Technical Document package for Biological License Approval of Kymriah®, which is one of the CAR-T products, lentiviral integration site analysis (LISA) has been applied to ensure quality and safety, including tumorigenicity information. In many cases, CAR vectors indicate CAR lentiviral vectors, and based on this, LISA could be applicable.

To assure quality, we must manufacture the products repeatedly, and these data should be used for the process validation.

For pre-clinical studies, the efficacy of HLA-knockdown/out iPS-derived T lymphocytes should be estimated using patient-derived xenograft model animals in addition to the *in vitro* efficacy test. The bio-distribution of the cells after administration should be examined to determine the distribution to un-intended organs/tissues and their survival duration. This knowledge could be useful for planning the toxicological safety tests, as it will determine which organs should be examined histologically and the times at which the experimental animals should be sacrificed. The products would be administrated via vein systemically, and the respiratory, central nervous, and cardiovascular systems should be evaluated according to a core battery test such as acute toxicology test in a manner similar to that used for small molecule conventional drugs.

After evaluation and confirmation of quality, safety, and feasible efficacy, we would submit our findings to the regulatory authorities and begin the clinical trials of HLA-knockdown/out iPS-derived T lymphocytes after approval.

7.4 Treatment of the Patient's Biological Data

In Japan, JACE® for severe burns, JACC® for arthritis, and TemCell-HS® for GVHD have been approved, and HeartSheet® for ischemic heart disease and Stemilac® for spinal cord injury have been granted conditional and time-limited approval under the PMD act. The approval system requires the pharmaceutical companies to submit the data of all patients who received the products to PMDA. Unfortunately, these data are limited to primary and secondary endpoints, and no big data could be obtained. All data shall be collected by the regulatory authority (PMDA). However, these data are not accessible by the scientific community. The data of patients enrolling in the clinical trials for regenerative medicinal products are also submitted only to PMDA.

Under the Regenerative Medicine Safety Act, a number of clinical trials using iPS cell-derived regenerative medicinal products have been initiated. This act has not ordered the principal investigators to submit the participant data.

7.5 Reform Efforts

According to Article 2 of the Supplementary Provisions for the Regenerative Medicine Safety Act, within 5 years after the entry into force of the law and considering the changes in the situation surrounding the law and the circumstances surrounding regenerative medicine, the necessary measures will be taken based on the effects of the law With the development of medical technology and the progress of research since the enactment of the law, the spread of new technologies that were not originally envisaged by the law has progressed. Specifically, gene therapy and genome editing technologies are expected to be widely used in the future according to the development and dissemination of these technologies. Scientific knowledge regarding the risks of individual regenerative medicine technologies has also been accumulated. The law provides for measures to ensure the safety of regenerative medicine and to consider bioethics. As of October 2019, there were 3792 protocols for treatments and 156 protocols for studies of regenerative medicine provision plans (excluding those that were discontinued or terminated), indicating that regenerative medicine has become widely available in Japan. In contrast, it has been observed that there is a large variation in quality, as many of these products do not guarantee effectiveness. In the current regulation for ensuring safety of regenerative medicine, a medical technique using a cell in which a gene is "introduced" or a cell obtained by subjecting the cell to culture or other processing corresponds to a technique that falls into the highest risk group in regenerative medicine. In contrast, genome editing technology is not included in this definition, as the gene is "not introduced" into the genome through the editing technique. Therefore, the genome-edited cells are classified into the lower risk group in regenerative medicine. Although the risks of genome editing technology have not yet been fully clarified, it is considered that

there are safety and ethical issues similar to those encountered in case of conventional gene manipulation technology. Regenerative medicine using genomic editing techniques shall be classified into the highest risk group in regenerative medicine in this reform of the Act.

The Regenerative Medicine Safety Act stipulates that "the safety and validity of regenerative medicine must be fully considered from an ethical and scientific point of view". The interpretation of validity is that it sufficiently predicts that effectiveness exceeds risk. To assess the relevance of regenerative medicine, the medical institutions are requested to submit annually an "evaluation sheet on safety and scientific validity of regenerative medicine" to the Certified Regenerative Medicine Committee. The relevant provisions of the act are based on the assumption that the number of patients, who should all be followed up, will be confirmed and estimated by the Certified Regenerative Medicine Committee to allow for the confirmation of the appropriateness of treatment. The specific contents of the provisions, however, are assumed to be currently insufficient to judge the appropriateness of treatment. The patient data should be collected to estimate the efficacy and safety of the protocols adequately. How the reporting framework in regard to registry should be reformed is currently under discussion.

7.6 Outlook: Human Germ Line Intervention Through Genome Editing

On December 18, 2019, the expert committee of the Ministry of Health, Labour, and Welfare released a report indicating that the regulation should be strengthened and include legislation to ban pregnancy and childbirth by human fertilization that has been using genome editing technology. In contrast, one governor within the Ministry of Health, Labour and Welfare is very cautious about legal restrictions on human embryos. The discussion started in November 2018 after Chinese researchers reported that they gave birth to twins from fertilized eggs that were less susceptible to the HIV virus due to genome editing. In Japan, there is a guideline[38] that prohibits clinical research on genome editing of fertilized eggs, but there are no legal restrictions on medical practices conducted within the discretion of the medical doctor under the Medical Practitioner's Law. The Clone Restriction Law enacted in 2001 prohibits the creation of human clones under penalties, but there is no law related to genome editing technology. Against this background, the technical committee[39] has proposed to the Ministry of Health, Labour and Welfare that the return of genetically

[38] Guideline for Gene Therapeutic Clinical Research. Notification No. 0228-2 issued on February 28th, 2019 by Minister's Secretariat Health Science Division, Ministry of Health, Labour and Welfare, Japan.

[39] Special Committee on Clinical Use of Human Fertilized Embryos Using Genome Editing Technology, etc., of the Science and Technology Subcommittee of the Health Science Council.

modified human fertilized eggs to the mother's body should be prohibited by law. In Japan, we have no information that genome editing of fertilized eggs has been performed. Additionally, there are expectations that genome-editing technologies could be applied in the treatment of genetic diseases in the future, and there is a concern that laws and regulations might inhibit the development of such technologies for patients. Adverse events associated with vertical transmission to off-springs are also envisaged, and it is not possible to estimate how many generations should be traced to ensure efficacy and safety. There is an opinion that the conventional medical philosophy of saving the current patient is not applicable. We know that genome editing technology is not the only way to avoid congenital incurable diseases. There is also preimplantation genetic diagnosis (PGD) on the basis of which only fertilized eggs that do not possess an adverse gene mutation are returned to the uterus after *in vitro* fertilization. The targetable diseases are limited but are applied clinically. There is a strong criticism that pre-implantation diagnosis is also a selection of life. Some philosophers speculate that the biological diversity created by nature is the basis of personal dignity and basic human rights regardless of cultural differences, and they believe that artificially rewriting genetic information upsets that diversity. We have many genome editing technologies, and they are constantly evolving. It is essential to evaluate the risks of mosaic effects and off-target and on-target insertions/deletions for each individual technology and to gain further social understanding.

7.7 Conclusion

Genome edited iPSC-derived regenerative medicine is regulated under the Pharmaceutical and Medical Device Act and the Regenerative Medicine Safety Act in Japan. The Pharmaceutical and Medical Device Act regulates regenerative medicines as cellular products and makes the availability of regenerative medicinal products on the market dependent on a biological license approval that must be acquired by the enterprises that are responsible for the placing on the market. The Regenerative Medicine Safety Act regulates regenerative medicines as techniques of medical doctors who deliver the medicine to the patients, and these doctors should have responsibility similar to that in organ transplantation. The available regenerative medicines to these doctors should resemble those that are defined by the hospital exemption of the EU. The genome edited-iPS cell-derived medicinal products or medicinal technique should be regulated under these Acts, respectively. Assuming that the genome edited iPS cell-derived regenerative medicines should be applied in clinical trials under the PMD Act, the products will be reviewed similar to ATMPs in the EU or biologics in the US. Also, assuming doctors would like to implement these medicines, the protocols should be reviewed by governmental review committees as high-risk medical techniques. The system resembles that of organ transplantation regarding the regulatory philosophy. The major difference in our system compared to that of the EU and the USA is that we have these two tracks for clinical application

in Japan, where one involves pharmaceutical regulation and the other involves organ/tissue/bone marrow transplantation. Notwithstanding the two tracks for clinical application, the genome edited-iPS cell-derived cells should be assessed for mosaic phenomena, off-target effects, and on-target insertion/deletion abnormalities in regard to the genomic structure, and they should also be assessed according to conventional regulatory requirements.

Acknowledgments This study was supported by the Grants-in-Aid by the Highway Program for Realization of Regenerative Medicine from the Japan Agency for Medical Research and Development (AMED) to AM.

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Chapter 8
Regulation of Genome Editing in Human iPS Cells: Republic of Korea

Yu-Cheol Shin

Abstract Regarding the regulation of genome editing of human iPS cells in Korea, the Bioethics Act (2004) and the Advanced Regenerative Medicine Act (2019) are of importance. The Korean Bioethics Act is premised on the principle that any conduct interfering with human dignity is prohibited. It sets the legal framework for genome editing of human iPS cells. The new Advanced Regenerative Medicine Act primarily lays down accelerated approval and authorization procedures and, at the same time, improves the protection of patients and subjects.

The main public authority competent for research and application of cell/gene therapies is the Korean Ministry of Food and Drug Safety. In contrast, the highest administrative authority for research on human materials and embryos as well as for genetic diagnoses and gene therapies is the Korean Ministry of Health which is charged with matters of bioethics and life safety. In addition, the National Bioethics Committee which is directly responsible to the President decides on the guiding principles of bioethics and life safety policy. The new Advanced Regenerative Medicine Act provides for the establishment of a commission tasked with policy advice on advanced medicinal products and advanced biologics.

In Korea, genome editing of human iPS cells is regulated in detail by statutory law, specifically with regard to the respective phases: (1) planning of non-clinical research, (2) sampling of human materials, (3) non-clinical studies concerning reprogramming, genome editing and re-differentiation, (4) clinical trials of gene therapy and gene therapy medicinal products, and (5) manufacturing and placing on the market of gene therapy medicinal products.

Personal data of patients and subjects may only be transmitted on the basis of written consent by the person concerned. This right to self-determination is enshrined in the general right to personality as guaranteed in the constitution.In accordance with the Korean Bioethics Act, direct interventions into the germ line are prohibited, even if they serve the purpose of curing a hereditary disease because, in accordance with the current state of science and technology, the risks of such interventions cannot be determined precisely.

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H.-G. Dederer, G. Frenken (eds.), *Regulation of Genome Editing in Human iPS Cells*, https://doi.org/10.1007/978-3-030-93023-3_8

8.1 Introduction

8.1.1 Clinical Trials for Somatic Gene Therapy in Korea

The following 23 clinical trials for somatic gene therapy have been or are being conducted in the Republic of Korea to date (as of December 2018) (Table 8.1).

8.1.2 Marketing Authorisation for Somatic Gene and Cell Therapy Products

The following 15 products have been approved for somatic cell therapy in the Republic of Korea (as of December 2018) (Table 8.2).

By contrast, only one gene therapy product (Invossa-K) has been approved so far in Korea on 12 July 2017. However, the approval was revoked by the Korean Ministry of Food and Drug Safety on 28 May 2019 because the cells transformed with TGF-β1 genes were not chondrocytes, as specified in the approval, but kidney cells (Table 8.3).[1]

Worldwide, the following 14 gene therapeutics have been approved to date (Table 8.4).

8.1.3 Research and Clinical Trials on Genome Editing

Research on cell therapies based on stem cells, in particular iPS cells, and on gene therapies using genome editing techniques, such as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), is in full swing, but no clinical study or experimental treatment using CRISPR methods has been carried out in Korea yet. Clinical studies on the use of CRISPR methods have so far been conducted mainly in the People's Republic of China (Table 8.5).

8.2 Genome Editing of Human iPS Cells: An Overview of the Regulatory Framework

For the regulation of genome editing of human iPS cells in Korea, the following two acts are of crucial importance:

[1] Cf. Korean Ministry of Food and Drug Safety (2019a).

Table 8.1 Clinical trials for somatic gene therapy in the Republic of Korea[a]

Trial ID	Title	Status
KR-0001	Interleukin 12 gene therapy of cancer by Peritumoural injection of transduced autologous fibroblasts	Closed (1997–1999)[b]
KR-0002	Phase I study for assessment of safety of angiogenic gene therapy with VMDA-3601 for the patients with critical limb ischemia	Closed (2001–2003)
KR-0003	Phase II study for assessment of efficacy of angiogenic gene therapy with VMDA-3601 for the patients with critical limb ischemia	Open (2004)
KR-0004	HLA-B7/beta2-microglobulin gene therapy of cancer by intra-tumoral injection	Closed (1995)[c]
KR-0005	Phase I study for assessment of safety of gene vaccine therapy with GX-12 in combination with HAART for the HIV-1 infected patients	Open (2005)
KR-0006	A phase I clinical study to evaluate safety and efficacy of JX-594 (thymidine kinase-deleted vaccinia virus plus GM-CSF) administered by Intratumoral injection in patients with hepatoma	Open (2005)
KR-0007	A phase I, dose-escalation, single-center study to assess the safety and tolerability of VM202RY in subjects with ischemic heart disease as an additional therapy to coronary artery bypass grafting	Open (2006)
KR-0008	A phase I study to determine the safety and biological Acitivity of cell mediated gene therapy using TissueGene-C in patients with degenerative joint disease of the knee prior to Total knee arthroplasty	Closed (2008)
KR-0009	An open-label, non-randomized, single-center, phase I/II trial to assess the safety and efficacy of single Administration of Autologous Hematopoietic Stem Cells Transduced with MT-gp91 retroviral vector in gp91 defective chronic granulomatous disease patients	Open (2007)
KR-0010	Comparative phase II study of replication-competent adenovirus-mediated suicide gene therapy in combination with radiation therapy versus radiation therapy alone for the treatment of newly-diagnosed, intermediate-to high-risk prostate cancer	Open (2007)
KR-0011	A single-center, randomized, open-label, dose escalating phase I study to evaluate the safety of intramuscularly administered DNA vaccine (HB-110) combined with Oral anti-viral (adefovir) in subjects with chronic hepatitis B over a 48-week period	Open (2007)
KR-0012	A phase II-a, open-label, randomized study of JX-594 (thymidine kinase-deleted vaccinia virus plus GM-CSF) administered by Intratumoral injection in patients with unresectable primary hepatocellular carcinoma	Open (2008)
KR-0013	A phase I study of Intratumoral Administration of DWP418 in refractory solid tumors	Open (2008)
KR-0014	Study of gene therapy for ischemic heart disease in Korea	Open (2010)
KR-0015	A single-blind, randomized, parallel-group, multi-center phase II study to determine the efficacy and safety of TissueGene-C mixed with fibrin-glue in patients with degenerative arthritis	Closed (2012–2015)
KR-0016	A randomized, open-label, multi-center, phase II clinical trial to determine the optimal dose and evaluate the safety of GX-188E, a DNA-based therapeutic vaccine, administered intramuscularly by	Open (2014)

(continued)

Table 8.1 (continued)

Trial ID	Title	Status
	electroporation (EP) in HPV type 16 and/or 18 positive patients with cervical intraepithelial neoplasia 3 (CIN 3)	
KR-0017	A single-center, open-label, accelerated titration, dose-escalating, phase I study to evaluate the safety and tolerability of IT injection GX-051, stem cell based gene therapeutics in patients with very advanced head and neck cancer	Open (2014)
KR-0018	A multicenter, single-blind, phase II-a clinical trial to evaluate the efficacy and safety of TissueGene-C, a cell-mediated gene therapy, in degenerative arthritis patients	Open (2015)
KR-0019	Clinical trial phase I for evaluation of tolerability and safety of replication-competent adenovirus-mediated double suicide gene therapy in combination with chemotherapy for the locally advanced pancreatic cancer	Open Date Closed (2016–2018)
KR-0020	Clinical trial phase I for evaluation of tolerability and safety of replication-competent adenovirus-mediated double suicide gene therapy in combination with chemotherapy for the locally advanced pancreatic cancer	Open (2016)
KR-0021	A phase II, multicenter, adaptive-design study to assess the safety and efficacy of VM202RY injected via percutaneous Transendocardial route in subjects with acute myocardial infarction	Open (2018)
KR-0022	Post marketing surveillance on safety and effectiveness evaluation of INVOSSA K injection	Open (2017)
KR-0023	A multicenter, randomized, placebo controlled, double-blind, parallel, phase III clinical trial to evaluate the efficacy and safety of Invossa K injection in patients diagnosed as knee osteoarthritis with Kellgren & Lawrence Grade 2	Open (2018)

[a]Cf. Gene Therapy Trials Worldwide (2019)
[b]Cf. Kang et al. (2001)
[c]Cf. Heo et al. (1998)

1. the Act of 29 January 2004 on Bioethics and Biosafety and
2. the Act of 27 August 2019 on Safety and Support for Advanced Regenerative Medicine and Advanced Biopharmaceuticals.

The Act of 29 January 2004 on Bioethics and Biosafety (the so-called Bioethics Act),[2] which was last amended on 23 April 2019, contains a total of 70 paragraphs and is divided into nine chapters:

1. General provisions (§§ 1–6)
2. National bioethics committee and institutional bioethics committees (§§ 7–14)

[2]An English translation of the Act as last amended on 12 December 2017 is available via https://www.law.go.kr/LSW/lsInfoP.do?lsiSeq=199534&viewCls=engLsInfoR&urlMode=engLsInfoR#0000.

Table 8.2 Approved cell therapy products in Korea[a]

No	Product	Manufacturer	Type	Indication	Date
1	Chondron	Sewon Cellontech	Autologous chondrocytes	Focal cartilage defect of knee	30.01.2001
2	Holoderm	Tego science	Autologous keratinocytes	Skin burn	10.12.2002
3	Kaloderm	Tego science	Allogeneic keratinocytes	Skin burn	21.03.2005
				Diabetic foot ulcer	24.06.2010
4	KeraHeal	Biosolution (formerly MCTT bio)	Autologous skin-derived keratinocytes	Skin burn	03.05.2006
5	CreaVax-RCC	JW CreaGene	Autologous dendritic cells	Metastatic renal cell carcinoma	15.05.2007
6	Immuncell-LC	Green cross cell	Autologous activated T-cell	Liver cancer	06.08.2007
7	RMS Ossron	Sewon Cellontech	Autologous osteoblasts	Focal bone formation	26.08.2009
8	Queencell	Anterogen	Autologous adipose tissue-derived adipose cell by minimal manipulation	Subcutaneous tissue defect	26.03.2010
9	Cure-skin Inj.	S.Biomedics	Autologous dermal fibroblasts	Depressed acne scar	11.05.2010
10	Cellgram	Pharmicell	Autologous bone marrow-derived mesenchymal stem cell	Left ventricular ejection fraction in acute myocardial infarction patients	01.07.2011
11	Cartistem	Medipost	Umbilical cord blood-derived mesenchymal stem cells	Knee articular cartilage defects in patients with osteoarthritis	18.01.2012
12	Cupistem	Anterogen	Autologous adipose tissue-derived mesenchymal stem cell	Crohn's fistula	18.01.2012
13	Neuronata-R	Corestem	Autologous bone marrow mesenchymal stem cell	Amyotrophic lateral sclerosis (Lou Gehrig's disease)	30.07.2014
14	KeraHeal-Allo	Biosolution (formerly MCTT bio)	Allogeneic skin-derived keratinocytes	Skin burn	16.10.2015
15	Rosmir	Tego science	Autologous fibroblasts	Nasojugal groove	27.12.2017

[a]Korean Ministry of Food and Drug Safety (2018a)

3. Research on human subjects and protection of human subjects of research (§§ 15–19)
4. Production of embryos and research thereon (§§ 20–35)

Table 8.3 Approved gene therapy products in Korea[a]

No.	Product	Manufacturer	Type	Indication	Date
1	Invossa-K Inj.	Kolon Life science	Allogenic chondrocytes from cartilage + allogenic chondrocytes from cartilage transformed with TGF-β1 genes	Osteoarthritis (Kellgren & Lawrence degree III)	27.12.2017; Revocation: 28.05.2019

[a]Korean Ministry of Food and Drug Safety (2019b)

Table 8.4 Approved gene therapy products worldwide[a]

No	Product	Date	Country	Vector	Indication
1	Gendicine	10/2003	China	Adenovirus	Head and neck cancer
2	Rigvir[b]	04/2004	Latvia	Echo-7 virus	Malignant melanoma
3	Oncorine	11/2005	China	Adenovirus	Head and neck cancer
4	Rexin-G	12/2007	Philippines	Retrovirus	Breast cancer, pancreatic cancer, oncologic metastasis
5	Neovasculgen	12/2011	Russia	Plasmid VEGF	Peripheral artery disease
6	Glybera	10/2012	EU	AAV	Lipoprotein lipase deficiency
7	Imlygic	10/2015	USA	Oncolytic virus	Malignant melanoma
8	Strimvelis	05/2016	EU	Retrovirus (ex vivo SC)	Severe combined immunodeficiency
9	Invossa-K[c]	07/2017	Korea	Retrovirus (hClonJb#7 C)	Osteoarthritis
10	Kymriah	08/2017	USA	Retovirus (anti-CD19 CAR-T)	Acute lymphoblastic B-cell leukemia (ALL)
11	Yescarta	10/2017	USA	Retovirus (anti-CD19 CAR-T)	Diffuse large B-cell lymphoma (DLBCL)
12	Luxturna	12/2017	USA	AAV2	Leber congenital amaurosis (LCA)
13	Zolgensma	05/2019	USA	AAV9	Spinal muscular atrophy (SMA)
14	Zynteglo	06/2019	EU	Lentivirus	β-Thalassemia

[a]Cf. Korean Ministry of Food and Drug Safety (2018b), p. 3
[b]The approval was revoked on 31 May 2019 (State Agency of Medicines, Republic of Latvia 2019)
[c]The approval was revoked on 28 May 2019 (Korean Ministry of Food and Drug Safety 2019a)

5. Research on human materials and human material banks (§§ 36–45)
6. Gene therapy, testing, etc. (§§ 46–53)
7. Supervision (§§ 54–59)
8. Supplementary provisions (§§ 60–63)
9. Penalty provisions (§§ 64–70)

Table 8.5 Clinical trials using CRISPR genome editing[a]

No	Identifier	Status	Study title	Location
1	NCT02793856	Active, not recruiting	PD-1 knockout engineered T cells for metastatic non-small cell lung cancer	China
2	NCT02863913	Withdrawn	PD-1 knockout engineered T cells for muscle-invasive bladder cancer	China
3	NCT02867332	Withdrawn	PD-1 knockout engineered T cells for metastatic renal cell carcinoma	China
4	NCT02867345	Withdrawn	PD-1 knockout engineered T cells for castration resistant prostate cancer	China
5	NCT02964481	Recruiting	Malignant hyperthermia registry and genetic testing	USA
6	NCT03044743	Recruiting	PD-1 knockout EBV-CTLs for advanced stage Epstein-Barr virus (EBV) associated malignancies	China
7	NCT03057912	Unknown	A safety and efficacy study of TALEN and CRISPR/Cas9 in the treatment of HPV-related cervical intraepithelial neoplasia I	China
8	NCT03081715	Completed	PD-1 knockout engineered T cells for advanced esophageal cancer	China
9	NCT03164135	Recruiting	Safety of transplantation of CRISPR CCR5 modified CD34+ cells in HIV-infected subjects with hematological malignances	China
10	NCT03166878	Recruiting	A study evaluating UCART019 in patients with relapsed or refractory CD19+ leukemia and lymphoma	China
11	NCT03167450	Suspended	Examining the knowledge, attitudes, and beliefs of sickle cell disease patients, parents of patients with sickle cell disease, and providers towards the integration of CRISPR in clinical care	USA (NHGRI)
12	NCT03332030	Recruiting	Stem cells in NF1 patients with tumors of the central nervous system	USA
13	NCT03342547	Recruiting	Identification of host factors of norovirus infections in mini-gut model	China (Hongkong)
14	NCT03398967	Recruiting	A feasibility and safety study of universal dual specificity CD19 and CD20 or CD22 CAR-T cell immunotherapy for relapsed or refractory leukemia and lymphoma	China
15	NCT03399448	Recruiting	NY-ESO-1-redirected CRISPR (TCRendo and PD1) edited T cells (NYCE T cells)	USA
16	NCT03538613	Withdrawn	Study of people with metastatic gastrointestinal epithelial cancer administering tumor-infiltrating lymphocytes in which the gene encoding CISH was inactivated using the CRISPR/Cas9 system	USA (NCI)

(continued)

Table 8.5 (continued)

No	Identifier	Status	Study title	Location
17	NCT03545815	Recruiting	Study of CRISPR-Cas9 mediated PD-1 and TCR gene-knocked out mesothelin-directed CAR-T cells in patients with mesothelin positive multiple solid tumors	China
18	NCT03606486	Recruiting	Lavage of the uterine cavity for diagnosis of ovarian cancer	USA
19	NCT03655678	Recruiting	A safety and efficacy study evaluating CTX001 in subjects with transfusion-dependent β-thalassemia	Canada/ Germany
20	NCT03681951	Terminated	First-time-in-human (FTIH) study of GSK3145095 alone and in combination with other anticancer agents in adults with advanced solid tumors	USA
21	NCT03690011	Not yet recruiting	Cell therapy for high risk T-cell malignancies using CD7-specific CAR expressed on autologous T cells	USA
22	NCT03728322	Not yet recruiting	iHSCs with the gene correction of HBB Intervent subjests with β-thalassemia mutations	China
23	NCT03745287	Recruiting	A safety and efficacy study evaluating CTX001 in subjects with severe sickle cell disease	USA
24	NCT03747965	Recruiting	Study of PD-1 gene-knocked out mesothelin-directed CAR-T cells with the conditioning of PC in mesothelin positive multiple solid tumors	China
25	NCT03855631	Active, not recruiting	Exploiting epigenome editing in kabuki syndrome: a new route towards gene therapy for rare genetic disorders (epi-KAB)	France
26	NCT03872479	Recruiting	Single ascending dose study in participants with LCA10	USA
27	NCT04035434	Recruiting	A safety and efficacy study evaluating CTX110 in subjects with relapsed or refractory B-cell malignancies	USA/Australia
28	NCT04037566	Recruiting	CRISPR (HPK1) edited CD19-specific CAR-T cells (XYF19 CAR-T cells) for CD19+ leukemia or lymphoma	China
29	NCT04074369	Recruiting	Evaluation of CRISPR-based test for the rapid identification of TB in pulmonary tuberculosis suspects	China
30	NCT04089891	Not yet recruiting	A study in patients with metastatic gastrointestinal epithelial cancer administering tumor-infiltrating lymphocytes in which the gene encoding CISH was inactivated using the CRISPR/Cas9 system	USA

[a]www.clinicaltrials.gov

The Korean Bioethics Act follows the principle[3] that any act that violates human dignity is unlawful and regulates the requirements related to genome editing of human iPS cells.

The Act of 27 August 2019 on Safety and Support for Advanced Regenerative Medicine and Advanced Biopharmaceuticals (so-called Advanced Regenerative Medicine Act) aims at promoting innovative development in the field of regenerative medicine and biopharmaceuticals. It contains a total of 63 paragraphs and is divided into seven chapters:

1. General provisions (§§ 1–4)
2. Establishment of the framework and implementation plan etc. (§§ 5–9)
3. Conduct and safety control of clinical trials for advanced regenerative medicine (§§ 10–22)
4. Approval and safety control of advanced biopharmaceuticals (§§ 23–38)
5. Supervision (§§ 39–46)
6. Supplementary provisions (§§ 47–56)
7. Penalty provisions (§§ 57–63)

Taking into account the particularities of advanced regenerative medicine and advanced biopharmaceuticals, the new Korean Advanced Regenerative Medicine Act provides for special rules for these medicinal products, which were hitherto insufficiently regulated under the Medical Service Act[4] and the Pharmaceutical Affairs Act[5] so far. Above all, it provides for accelerated approval and licensing procedures and, at the same time, increased protection of the patients concerned.

8.3 Regulatory Prerequisites for Combined Gene/Cell Therapy Using Genome-Edited Human iPS Cells to Be Differentiated into Somatic Cells for Autologous Retransplantation

8.3.1 Administrative Authorities

The main authority responsible for research on and application of cell/gene therapies is the Korean Ministry of Food and Drug Safety, which was separated from the

[3] Cf. Art. 10 Constitution of the Republic of Korea of 29 October 1987, available via http://www.law.go.kr/lsInfoP.do?lsiSeq=61603&urlMode=engLsInfoR&viewCls=engLsInfoR#.

[4] Cf. the Act on Medical Service of 20 March 1962, last amended on 27 August 2019; see the English translation of this Act as last amended on 30 November 2016: http://www.law.go.kr/lsInfoP.do?lsiSeq=183558&urlMode=engLsInfoR&viewCls=engLsInfoR#0000.

[5] Cf. the Act on Pharmaceutical Affairs of 28 December 1953, last amended on 15 January 2019; see the English translation of this Act as last amended on 2 December 2016: http://www.law.go.kr/lsInfoP.do?lsiSeq=188093&urlMode=engLsInfoR&viewCls=engLsInfoR#0000.

Ministry of Health in 2013[6] and has since been directly subordinate to the Prime Minister.

The Korean Ministry of Health (Ministry of Health and Welfare[7]) is nevertheless responsible for bioethics and life safety matters so that it is the supreme administrative authority for the research on human materials (i.e. the physical components of human beings such as organs, cells, blood, body fluids etc. and the sera, plasmas, chromosomes, DNA, RNA, proteins etc. separated from these) and embryos as well as for genetic tests and gene therapies.[8]

In addition, the National Bioethics Committee, which is directly subordinate to the President and has 16 to 20 members,[9] determines the general policy concerning bioethics and life safety.[10]

The new Advanced Regenerative Medicine Act provides for the establishment of a committee for policy advice on advanced regenerative medicine and advanced biopharmaceuticals.[11] It shall have a maximum of 21 members and report directly to the Minister of Health.[12] Its main task will be to advise on the establishment of the five-year framework and the annual implementation plan.[13]

8.3.2 Control Mechanisms

8.3.2.1 Non-Clinical Research Planning

Every researcher who wants to conduct research on human materials must submit his research plan to the bioethics committee of his institution (i.e. the research institute, university, clinic, biobank, biotechnological company etc.) and obtain the committee's approval before starting his research.[14] The institutional bioethics committee,

[6] Cf. § 25 Act on Government Organization of 23 March 2013, last amended on 8 June 2018; see the English translation of this Act as last amended on 1 January 2016: http://www.law.go.kr/lsInfoP.do?lsiSeq=177655&urlMode=engLsInfoR&viewCls=engLsInfoR#0000.

[7] Cf. §§ 26 and 38 Government Organization Act (see fn. 6).

[8] Cf. §§ 8, 10 et seqq., 22, 29 et seq., 33 et seq., 36, 41, 48 et seqq., 54 et seqq., 60 et seqq. Bioethics Act (see fn. 2).

[9] Six ministers (of Education, Science and ICT, Justice, Trade and Industry, Health and Welfare, Gender Equality and Family), up to seven experts (in life sciences, medicine, social sciences) and up to seven representatives of society (religions, ethics, law, NGOs).

[10] Cf. §§ 7 et seqq. Bioethics Act (see fn. 2).

[11] Cf. § 7 Advanced Regenerative Medicine Act.

[12] Cf. § 7 par. 2 and 3 Advanced Regenerative Medicine Act.

[13] Cf. § 7 par. 1 Advanced Regenerative Medicine Act.

[14] Cf. § 36 Bioethics Act (see fn. 2).

which must have at least five members including one external,[15] examines if the research plan is unobjectionable from an ethical perspective only.

Small institutes that have less than five researchers or whose committee has examined less than 30 applications within 3 years may instruct the bioethics committee of another institution to examine their research plans.[16] Researchers who do not belong to any institute may apply for approval to a joint institutional bioethics committee designated as such by the Minister of Health.[17]

8.3.2.2 Extraction of Human Materials

Every researcher who wishes to conduct research on human materials must, prior to their extraction, provide the donor with sufficient information and obtain written consent on the manner of obtaining and the treatment of the materials concerned (e.g. cells, blood, body fluids etc.) as well as on the following facts:

1. research purpose,
2. protection and treatment of personal information,
3. storage and destruction of the materials concerned,
4. transfer of the materials or disclosure of genetic information obtained from them,
5. revocation of consent, treatment of the acquired materials in the event of revocation of consent, the donor's right to be informed about the progress and outcome of the research and
6. destruction or transfer of the materials in the event of interruption of the research.[18]

The donor may freely determine the storage period, the possibility and conditions of transfer as well as the anonymisation of personal information and may freely revoke his or her consent.[19]

If the donor is incapable of giving consent or his or her ability to give consent is limited, the consent of his or her legal representative, spouse, or relative in the ascending or descending line is required.[20]

[15] Cf. § 11 Bioethics Act (see fn. 2).—This does not apply if the research purpose is changed. In practice, however, such cases are very rare because the purpose of the research is formulated very comprehensively from the outset, e.g. curing hereditary or serious diseases or improving the health care system.

[16] Cf. § 10 par. 2 Bioethics Act (see fn. 2) and § 5 ministerial ordinance for implementing the Bioethics Act.

[17] Cf. § 12 par. 1 no. 2 Bioethics Act (see fn. 2).

[18] Cf. § 37 par. 1 Bioethics Act (see fn. 2) and § 34 ministerial ordinance for implementing the Bioethics Act.

[19] Cf. Form No. 34 in the annex to the ministerial ordinance for implementing the Bioethics Act.

[20] Cf. § 37 par. 2 in conjunction with § 16 par. 2 Bioethics Act (see fn. 2).

If the researcher receives human materials from another researcher or institution and the donor has already given written consent in the above sense, in particular for the transfer, the researcher does not require additional consent from the donor.[21]

The new Advanced Regenerative Medicine Act provides for the establishment of institutions for the treatment of cells for advanced regenerative medicine.[22,23] If these institutions wish to extract human cells for the purpose of transferring them to clinics carrying out clinical trials for gene therapy or of gene therapy products, they must obtain written consent from the donor concerning the following matters:

1. purpose and method of cell extraction,
2. protection and treatment of personal information,
3. taking note of and verification of the medical history,
4. transfer, storage and destruction of extracted cells etc. and
5. revocation of consent etc.[24]

8.3.2.3 Non-Clinical Studies on Reprogramming, Genome Editing, Redifferentiation

Every researcher already having received the approval of the institutional bioethics committee for her research plan can freely reprogramme the cells extracted from human materials into iPS cells, edit the genome of the iPS cells, e.g. using CRISPR/Cas, and re-differentiate the genome-edited iPS cells into somatic cells or progenitor cells. This is not regulated in Korea.

The Korean Ministry of Food and Drug Safety and its subordinate National Institute of Food and Drug Safety Evaluation publish guidelines on non-clinical assessment of gene therapy products (2017), DNA vaccines (2015), stem cell therapy products (2014) etc. which, although not directly legally binding, impose obligations on researchers and institutions by requiring them to attach the documentation on non-clinical studies to the application for approval of clinical trials as well as to the application for market authorisation of a biologic.[25] These guidelines

[21] Cf. § 37 par. 3 Bioethics Act (see fn. 2).

[22] The Korean legislature defines the term "advanced regenerative medicine" as cell therapies, gene therapies and tissue engineering, cf. § 2 no 1 Advanced Regenerative Medicine Act.

[23] Cf. § 15 Advanced Regenerative Medicine Act.

[24] Cf. § 16 Advanced Regenerative Medicine Act.

[25] Cf. § 5 par. 4 no. 4 ministerial ordinance on the authorisation of clinical trials of medicinal products of 3 December 2002, last amended on 24 May 2019; § 6 ministerial ordinance on testing of biologics for marketing authorisation of 23 May 2003, last amended on 9 September 2019.

contain, similar to the EU[26] and US[27] guidelines, in particular the requirements concerning toxicity tests (single and repeated dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, immunotoxicity and local immunotolerance etc.) and pharmacological tests (efficiency, biodistribution, persistence, integration analysis etc.).

8.3.2.4 Clinical Studies of Gene Therapies and Gene Therapy Products

According to the Korean Bioethics Act, gene therapy, whether *in vivo* or *ex vivo*,[28] may only be researched (1) if the research aims at curing a hereditary disease, cancer, an acquired immune deficiency syndrome (AIDS), or a disease that threatens human life or causes severe disability, or (2) if no possible therapy exists or a significantly better therapy may be expected compared to existing therapies.[29] Gene therapy on embryos, sperm, oocytes and foetuses is prohibited.[30]

According to the new Advanced Regenerative Medicine Act, any clinic wishing to conduct clinical trials for a gene therapy or of gene therapy products must be qualified by the Minister of Health as advanced regenerative medicine clinic.[31] The prerequisites for this are the necessary facilities, equipment and personnel.[32]

The new Advanced Regenerative Medicine Act provides for the establishment of a review commission for advanced regenerative medicine and advanced biopharmaceuticals.[33,34] This commission shall have a maximum of 20 members[35]

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[26] Cf. European Medicines Agency, Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (13 April 2012), EMA/CAT/GTWP/671639/2008, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically-modified_en.pdf.

[27] Cf. Food and Drug Administration, Guidance for Industry, Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products (August 2015), https://www.fda.gov/media/89036/download.

[28] Cf. § 2 No 16 and § 47 par. 2 Bioethics Act (see fn. 2). The Korean legislature differentiates between cell therapy and gene therapy to the effect that cell therapy only applies if there has been no genetic manipulation.

[29] Cf. § 47 par. 1 Bioethics Act (see fn. 2).

[30] Cf. § 47 par. 3 Bioethics Act (see fn. 2).

[31] Cf. § 10 par. 1 Advanced Regenerative Medicine Act.

[32] Cf. § 10 par. 2 Advanced Regenerative Medicine Act.

[33] The Korean legislature defines the term "advanced biopharmaceuticals" as cell therapy products, gene therapy products and tissue engineering products as well as biopharmaceuticals physically and/or chemically fused or converged with a medical device, cf. § 2 no. 5 Advanced Regenerative Medicine Act.

[34] Cf. § 13 Advanced Regenerative Medicine Act.

[35] Cf. § 13 par. 2 Advanced Regenerative Medicine Act. The members of this commission are appointed by the Minister of Health after consultation with the Minister of Food and Drug Safety.

and will be responsible for examining the research plans of the clinical trials for advanced regenerative medicine and for evaluating advanced biopharmaceuticals.[36]

Any clinic wishing to carry out clinical trials for gene therapy or of gene therapy products must submit its research plan for clinical trials in advance to the above-mentioned review commission.[37] The review commission examines the research plans with regard to (1) scientific and ethical concerns, urgency and necessity of the study, (2) appropriateness of the choice and number of test subjects, (3) adequacy of the protective measures for test subjects etc.[38] and decides whether a long-term follow-up is necessary.[39] Based on this assessment, any research plan envisioning clinical trials for gene therapy or of gene therapy products must be approved by the Minister of Food and Drug Safety.[40]

The Korean Advanced Regenerative Medicine Act categorises clinical trials for gene therapy or of gene therapy products into three classes according to the risks they entail:[41] class A for very dangerous clinical trials, class B for dangerous clinical trials, and class C for less dangerous clinical trials.

If clinics, which are qualified as advanced regenerative medicine clinics, wish to conduct clinical trials in class A or B, they must be supplied with the required cells etc. by an institution for the treatment of cells for advanced regenerative medicine established under the Advanced Regenerative Medicine Act.[42] Only class C clinical trials may be conducted using cells acquired and treated by themselves.[43]

Clinics wishing to conduct clinical trials for gene therapy or of gene therapy products must sufficiently explain concerned the following facts to the patients and comparators and obtain their written consent in advance:[44]

1. purpose and content of the study,
2. expected results and possible side effects,
3. compensation for damages and losses incurred through participation in the study,
4. protection and disclosure of personal information,
5. possibility of revocation and
6. notification of side effects, long-term follow-up, subsequent measures etc.

Clinics wishing to conduct clinical trials for gene therapy or of gene therapy products are obliged to take out liability insurance in order to ensure the compensation of participants in clinical trials.[45]

[36] Cf. § 13 par. 1 Advanced Regenerative Medicine Act.
[37] Cf. § 12 par. 1 Advanced Regenerative Medicine Act.
[38] Cf. § 14 par. 2 Advanced Regenerative Medicine Act.
[39] Cf. § 14 par. 1 Advanced Regenerative Medicine Act.
[40] Cf. § 14 par. 3 Advanced Regenerative Medicine Act.
[41] Cf. § 2 no. 3 Advanced Regenerative Medicine Act.
[42] Cf. § 15 Advanced Regenerative Medicine Act.
[43] Cf. § 10 par. 3 Advanced Regenerative Medicine Act.
[44] Cf. § 11 par. 1 Advanced Regenerative Medicine Act.
[45] Cf. § 11 par. 4 Advanced Regenerative Medicine Act.

According to the Advanced Regenerative Medicine Act, the Minister of Health shall establish an institute for safety control of advanced regenerative medicine.[46] It shall supervise advanced regenerative medicine clinics, collect and manage information from clinical trials for advanced regenerative medicine and establish a system for investigating side effects and long-term follow-up.[47]

8.3.2.5 Manufacture and Marketing of Gene Therapy Products

Anyone wishing to commercially produce advanced biopharmaceuticals requires an authorisation from the Minister of Food and Drug Safety (the so-called manufacture authorisation).[48] Furthermore, anyone wishing to place advanced biopharmaceuticals manufactured by him or her or by a third party on his or her behalf requires an approval of the biopharmaceuticals by the aforementioned Minister (the so-called marketing authorisation).[49] In this case, the applicant must submit the following documentation when applying for a marketing authorisation:

1. documentation regarding the safety and efficacy of the biopharmaceuticals,
2. documentation on manufacture standards as well as quality control standards and testing methods,
3. documentation on the assessment of manufacture and quality control processes,
4. documentation on the plan for the safe use and hazard control of the biopharmaceuticals,
5. documentation on medical devices in the case of amalgamated or converted biopharmaceuticals, as well as
6. the documentation required for approval and safety control in accordance with an ordinance issued by the Prime Minister.[50]

Anyone wishing to place biopharmaceuticals manufactured a third party on his or her behalf on the market commercially must register with the abovementioned Minister.[51] In any case, he or she requires a marketing authorisation for the respective biopharmaceuticals.

An advanced biopharmaceutical manufactured for the purpose of clinical trials may be used in clinical trials without manufacturing authorisation and marketing authorisation if the Prime Minister's ordinance so provides.[52]

[46] Cf. § 19 par. 1 Advanced Regenerative Medicine Act.
[47] Cf. § 19 par. 2 Advanced Regenerative Medicine Act.
[48] Cf. § 23 par. 1 Advanced Regenerative Medicine Act.
[49] Cf. § 23 par. 2 Advanced Regenerative Medicine Act.
[50] Cf. § 23 par. 2 Advanced Regenerative Medicine Act.
[51] Cf. § 23 par. 3 Advanced Regenerative Medicine Act.
[52] Cf. § 23 par. 5 Advanced Regenerative Medicine Act.

Anyone wishing to import advanced biopharmaceuticals commercially from abroad must equally register with the abovementioned Minister. Depending on the respective biopharmaceuticals, a marketing authorisation may be required.[53]

According to the Advanced Regenerative Medicine Act, the Minister of Food and Drug Safety shall set up a centre for regulatory science of advanced biopharmaceuticals in form of a foundation.[54] The centre shall set up an electronic network to collect and manage information on manufacture, supply and use of advanced biopharmaceuticals, collect and analyse national and international information on the development of advanced biopharmaceuticals as well as develop state-of-the-art guidelines and train professionals in manufacture and quality control of advanced biopharmaceuticals.[55]

The new Advanced Regenerative Medicine Act provides for an accelerated approval procedure for advanced biopharmaceuticals.[56] The Minister of Food and Drug Safety may, on application, determine an accelerated marketing authorisation procedure

1. if no alternative medicinal products exist and the biopharmaceutical in question is intended to cure a life-threatening or serious disease such as cancer
2. if the purpose is to cure a rare disease within the meaning of the Rare Disease Management Act,[57] or
3. if the purpose is to prevent or cure an infectious disease caused by biological terrorism or an infectious disease threatening as an epidemic within the meaning of the Infectious Disease Control and Prevention Act.[58,59]

Under the accelerated approval procedure, a decision must be taken within 60 days.[60]

[53] Cf. § 27 par. 1 Advanced Regenerative Medicine Act.

[54] Cf. § 32 par. 1 and 2 Advanced Regenerative Medicine Act.

[55] Cf. § 32 par. 3 Advanced Regenerative Medicine Act.

[56] Cf. § 36 Advanced Regenerative Medicine Act.

[57] Cf. the Act on Rare Disease Management of 29 December 2015, last amended on 30 April 2019; see the English translation of this Act as last amended on 29 December 2015: http://www.law.go.kr/lsInfoP.do?lsiSeq=178255&urlMode=engLsInfoR&viewCls=engLsInfoR#0000.

[58] Cf. the Act on Infectious Disease Control and Prevention of 28 February 1957, last amended on 31 December 2018; see the English translation of this Act as last amended on 2 December 2016: http://www.law.go.kr/lsInfoP.do?lsiSeq=188080&urlMode=engLsInfoR&viewCls=engLsInfoR#0000.

[59] Cf. § 36 par. 2 Advanced Regenerative Medicine Act.

[60] Cf. § 36 par. 3 Advanced Regenerative Medicine Act.

8.4 Treatment of Patient Biological Data

The protection of personal data is regulated in detail both in the Bioethics Act[61] and in the Advanced Regenerative Medicine Act.[62] In addition, the Personal Information Protection Act[63] applies, if no other law contains special provisions. The personal data of patients and test persons may only be transferred with the written consent of the person concerned.[64] In this case, they must be anonymised, unless the respective person has expressly agreed in advance to disclose his or her personal data to a third party in a non-anonymised manner.[65] In Korea, every patient or test person can therefore freely determine if and how his or her personal data will be treated. This right of self-determination over personal data is even constitutionally protected as general right of privacy.[66]

8.5 Reform Efforts

Since the Advanced Regenerative Medicine Act was promulgated in August 2019 and did not enter into force until 28 August 2020, there are currently neither reform efforts nor criticism of the new Act in Korea.

8.6 Outlook: Human Germ Line Intervention through Genome Editing

According to the Bioethics Act, direct interventions in the human germ line are prohibited, even if they are intended to cure a hereditary disease.[67] According to the guidelines for gene therapy products, indirect interventions in the human germ line must also be avoided (so-called genotoxicity testing).

In my opinion, the reasons for prohibiting germ line therapy and avoiding genotoxicity are not that such interventions violate human dignity, which is inviolable, but rather that the risks of such interventions cannot be precisely estimated according to the current state of science and technology. Once genetic engineering

[61] Cf. §§ 16, 18, 24, 37, 42, 51 Bioethics Act (see fn. 2).

[62] Cf. §§ 11, 16, 29 Advanced Regenerative Medicine Act.

[63] Cf. the Act on Personal Information Protection of 29 March 2011, last amended on 26 July 2017; see the English translation of this Act as last amended on 26 July 2017: http://www.law.go.kr/lsInfoP.do?lsiSeq=195062&urlMode=engLsInfoR&viewCls=engLsInfoR#0000.

[64] Cf. § 18 par. 1 Bioethics Act (see fn. 2).

[65] Cf. § 18 par. 2 Bioethics Act (see fn. 2).

[66] Cf. Art. 10 and 17 Korean Constitution (see fn. 3).

[67] Cf. § 47 par. 3 Bioethics Act (see fn. 2).

has been developed to such an extent that the risks of germ line correction could be accurately assessed, germ line editing should be allowed to cure of certain hereditary diseases. For in this case, one cannot reasonably claim that curing a hereditary disease would violate the patient's dignity.

8.7 Conclusion

In Korea, it remains to be seen how the new Advanced Regenerative Medicine Act will be implemented. The new statutory requirement to establish an institute for safety control of advanced regenerative medicine and a centre for regulatory science of advanced biopharmaceuticals will hopefully contribute to the development of regenerative medicine and gene therapy in Korea.

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Chapter 9
Comparative Analysis

Hans-Georg Dederer

Abstract The country reports (Chaps. 3–8) form the essential basis of this final chapter. It provides a comparative analysis the purpose of which is to identify best regulatory practices with a view to the science-based (*cf.* Chap. 2) regulation of somatic cell/gene therapies based on genome-edited iPSCs, germ line therapies and biological data protection. The comparative analysis, first, refers to general aspects (*i.e.* the overall structure of the applicable national, European and international legal frameworks and the competent authorities on the domestic and EU level). It, then, turns to two fundamental steps of the translational pathway from research to marketable somatic cell/gene therapy products, *i.e.* clinical trials and placing on the market. Regarding these two steps, the comparative focus is on in advance control instruments, consultation mechanisms, timelines, expedited reviews, manufacturing prerequisites, and requirements specifically addressed to the use of genetically modified organisms (GMOs). In addition, the comparative analysis relates to treatments in the absence of prior marketing authorizations for the medicinal products administered to the patients concerned. Such therapeutic treatments may benefit individual patients or particular patient groups. They have received peculiar designations such as, *inter alia*, 'hospital exemption', 'special needs exemption', 'compassionate use exemption' or 'expanded access use'. Regarding germ line therapies, the comparative analysis reveals different regulatory concepts which, nevertheless, aim consonantly at prohibitions either *de iure* or *de facto*. With a view to the treatment of patient biological data, the country reports bare considerable regulatory diversity. The chapter rounds off with identifying, albeit somewhat tentatively, best regulatory practices relating to genome-edited iPSC-based somatic cell/gene therapies, germ line therapies and protection of patients' biological data.

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H.-G. Dederer, G. Frenken (eds.), *Regulation of Genome Editing in Human iPS Cells*, https://doi.org/10.1007/978-3-030-93023-3_9

9.1 Introduction

The following comparative analysis is based, primarily, on the country reports in this volume[1] and, to a certain extent, especially as regards this chapter's overall structure, on a study[2] prepared upon request by the Commission of Experts on Research and Innovation (EFI)[3] established by the German Federal Ministry of Education and Research (BMBF).[4]

The purpose of this comparative analysis is to identify regulatory approaches, structures, techniques and models which have been developed by the jurisdictions under review, *i.e.* the European Union (EU), France (F), Germany (D), Japan (J), Korea (ROK), Switzerland (CH) and the United States (USA), in order to regulate somatic cell/gene therapies, germ line therapies and biological data protection. Such a comparative analysis may allow for the identification of best regulatory practices. Admittedly, the notion of 'best regulatory practices' is rather vague. This vagueness implies that the best regulatory practices are ascertained, in the end, through value judgments which are, by their very nature, always somewhat subjective and, at least to a certain extent, discretionary.[5] This also applies to the benchmark for best regulatory practices. It is the choice of this chapter's author that the benchmark should be the optimal contribution of regulatory practices to the translation of basic research into clinical applications, especially with a focus on genome-edited iPSC-based somatic cell/gene therapies. Accordingly, best regulatory practices are those which do not impede but rather support research on, and development of, treatments of hereditary, often severe and hitherto incurable, diseases. For the purpose of identifying best regulatory practices, one has to take into account as well that the development of such highly innovative cell/gene therapies requires research involving human beings who must not be put at unwarranted risks to life and health. Against this background, regarding genome-edited iPSC-based somatic cell/gene therapies, best regulatory practices should be strictly science-based, require a thorough risk-benefit analysis, support academic researchers, investigators and sponsors, and provide for oversight mechanisms which are not more restrictive than necessary.

With these criteria in mind, the comparative analysis will relate, first, to the overall legal and institutional structures (*infra* Sect. 9.2). The analysis will, then, turn to the regulation of clinical trials (*infra* Sect. 9.3) and the placing on the market of somatic cell/gene therapy products (*infra* Sect. 9.4). Special sections will be devoted to treatments of patients with somatic cell/gene products which have not, or not yet, been authorized for placing on the market (*infra* Sect. 9.5) and to legal issues of personal data protection arising from the use of patient-specific biological

[1] Chapters 3–8.

[2] Dederer and Frenken (2021).

[3] Expertenkommission Forschung und Innovation.

[4] Bundesministerium für Bildung und Forschung.

[5] Regarding the problem of how to identify best regulatory practices see, in brief, Dederer and Hamburger (2019), pp. 8–9.

data (*infra* Sect. 9.6). The next section will deal with the highly controversial issue of germ line therapies (*infra* Sect. 9.7). The final section will try to draw conclusions from the foregoing comparative analysis by summarizing, tentatively, what could be considered best regulatory practices (*infra* Sect. 9.8).

9.2 General Aspects

For the purposes of this comparative analysis, the general aspects to be compared encompass, on the one hand, formal and substantive facets of the regulatory frameworks concerned (*infra* Sect. 9.2.1) and, on the other hand, institutional facets as regards the sometimes complex network of authorities, agencies and commissions involved (*infra* Sect. 9.2.2).

9.2.1 Legal Frameworks

When comparing the legal frameworks of the jurisdictions under review, one may distinguish formal aspects (*infra* Sect. 9.2.1.1) from substantive aspects (*infra* Sect. 9.2.1.2). Formal aspects concern the sources of law, the several layers, including the hierarchy, of norms as well as regulatory peculiarities related to federal systems of government. Substantive aspects, on the other hand, refer to the subject-matter of the applicable laws and regulations.

9.2.1.1 Formal Aspects

Genome-edited iPSC-based cell/gene therapies are governed, to a varying degree, by a multi-level framework made up of national law, EU law and international law.

9.2.1.1.1 National Law

The general structure of the national legal frameworks under review is, *grosso modo*, very similar. The most relevant sources of law are, first, statutes enacted by the legislature[6] and, second, rules adopted by the executive which may be called, or translated into English as, ‘regulations’, ‘decrees’, ‘ordinances’ etc. In addition,

[6]The most important statutes related to somatic cell/gene therapies based on genome-edited iPSCs being: CH: Human Research Act, Therapeutic Products Act; D: Medicinal Products Act; F: Public Health Code; J: Pharmaceuticals and Medical Devices Act, Regenerative Medicine Safety Act, ROK: Advanced Regenerative Medicine Act; USA: Federal Food, Drug, and Cosmetic Act, Public Health Service Act.

guidelines or guidance notes issued by regulatory or scientific agencies may apply. Such guidelines or guidance notes can be characterized as 'soft law' since they do not lay down legally binding rules ('hard law') but are, nevertheless, expected to be followed in practice and, thus, may be considered to be binding *de facto*. Formally speaking, they do not constitute sources of law, though.[7]

Accordingly, the rules applicable to somatic cell/gene therapies based on genome-edited iPSCs are distributed across three layers of norms which, at the same time, form a hierarchy of norms. The first layer, on top of the hierarchy, is made up of laws enacted by parliament. These acts of parliament are complemented, on a second layer, by rules adopted by the executive, *i.e.* by the government, ministries or regulatory agencies. A third layer of norms consists of the aforementioned guidelines or guidance notes.[8]

In exceptional cases, rules specifically applicable to the life sciences, *e.g.*, provisions on medical research involving human beings, on genetic modifications of human beings or on cell and tissue transplantation, have been incorporated into the national constitution, *i.e.*, regarding the national hierarchy of norms, into the supreme layer of norms. As regards the countries reviewed, this applies to Switzerland only.[9]

Of course, all constitutions of the countries under review[10] contain norms, especially fundamental rights, which may have[11] a significant bearing on legislatures when making, *e.g.*, medicinal products law as well as on administrative authorities and courts when interpreting and applying the law. As regards genome-edited iPSC-based somatic cell/gene therapies, germ line therapies and treatment of patient biological data, pertinent fundamental rights are, *inter alia*, the rights to human dignity, to life, to physical integrity, to personal data protection, to equal treatment etc.

[7] The notion 'sources of law' is limited to those phenomena which provide legally binding norms, *i.e.* legally binding rules which are generally applicable and which form standards for (*e.g.*, judicial) review of legality. Accordingly, on the national level, the most important sources of law are the constitutions, statutes (enacted by parliament) and regulations (adopted by the administration).

[8] Although these guidelines or guidance notes are not legally binding they can, nevertheless, be considered to lay down 'norms' in a broader sense because, *e.g.*, academic researchers or investigators and sponsors of clinical trials or pharmaceutical enterprises are, as a rule, expected to comply with these guidelines or guidance notes respectively.

[9] See, in particular, Articles 118b, 119 and 119a of the Swiss Federal Constitution and, for an analysis of these provisions, Schweizer et al., Chap. 5, Sect. 5.2.1.1.3 (this volume).

[10] With the notable exception of France the constitution of which refers only in its preamble to the famous 'Déclaration des droits de l'homme et du citoyen' of 1789. However, according to Decision No. 71-44 DC of 16 July 1971 of the Conseil Constitutionnel, the fundamental rights enshrined in the 'Déclaration' may serve as constitutional standards for judicial review of acts of parliament.

[11] Depending on constitutional law doctrine and jurisprudence of the respective jurisdiction.

9.2.1.1.2 EU Law

Another special case are the Member States of the European Union (EU), *i.e.*, among the countries under review, France and Germany. Although EU Member States are still sovereign entities under general public international law, they have empowered the EU to adopt laws which are binding upon the Member States and, as the case may be, also on individuals, *i.e.* natural or legal persons.[12] For reasons of uniform application of EU law throughout the whole Union, EU law prevails over national, including constitutional, law.[13] EU Regulations are directly applicable within the Member States (Article 288(2) TFEU), whereas EU Directives must be implemented into national law by the Member States (*cf.* Article 288(3) TFEU).[14] Depending on the individual case, also EU Decisions (Article 288(4) TFEU) may be directly applicable, otherwise they must be implemented into national law.

In accordance with the principle of limited attributed powers (Article 5(2) TEU), the EU does not have plenary legislative authority. In particular, with regard to public health policy, Member States have conferred upon the EU only very narrowly tailored competences (*cf.* Article 168 TFEU). This does not apply to medicinal products, though (*cf.* Article 168(4)(c) TFEU). Therefore, the EU legislature, *i.e.* the Council of the EU and the European Parliament (*cf.* Article 294 TFEU), enacted several Regulations and Directives pertinent in the field of somatic cell/gene therapies based on genome-edited iPSCs.[15] In addition, the European Commission, which can be considered the main executive organ of the EU (*cf.* Article 17 TEU), adopted Regulations and Directives (*cf.* Article 290, 291 TFEU), too. Furthermore, the European Medicines Agency (EMA), which is a scientific agency, issued several relevant guidelines. Accordingly, also on the EU level, the legal framework is three-layered: first, Regulations and Directives enacted by Council and Parliament, second, Regulations and Directives adopted by the Commission, and, third, guidelines issued by EMA.

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[12] The sources of EU law are the Treaties, *i.e.* the Treaty on European Union (TEU) and the Treaty on the Functioning of the European Union (TFEU), as well as Regulations, Directives and Decisions (Article 288(2)–(4) TFEU).

[13] CJEU, C-6/64, Costa v E.N.E.L., ECLI:EU:C:1964:66, ECR 1964, 585 (593–594); regarding, especially, supremacy of EU law over national constitutional law see CJEU, C-11/70, Internationale Handelsgesellschaft mbH v Einfuhr- und Vorratsstelle für Getreide und Futtermittel, ECLI:EU:C:1970:114, para. 3.

[14] Only in exceptional cases, according to the CJEU's jurisprudence (CJEU, C-8/81, Becker, ECLI:EU:C:1982:7, paras. 21–25), Directives may be directly applicable within the domestic legal order of Member States as well.

[15] The most important being: Human Medicines Code Directive 2001/83/EC, Biotech Medicinal Products Regulation (EC) No. 726/2004, ATMP Regulation (EC) No. 1394/2007, Clinical Trials Directive 2001/20/EC. The Clinical Trials Directive is to be replaced by the new Clinical Trials Regulation (EU) No. 536/2014 which will be applicable as of January 31, 2022. On the new Clinical Trials Regulations, in brief, see Mahalatchimy, Chap. 4, Sect. 4.3.3 (this volume); Frenken and Lüttge, Chap. 3, Sect. 3.5 (this volume).

Although EU law may be implemented and enforced by EU organs, *e.g.* by the European Commission, it is, in the very first place, the Member States' task to implement and enforce EU law (*cf.* Article 291 TFEU). In addition, in accordance with the principle of loyalty (Article 4(3) TEU), the Member States' administrative authorities and courts have to construe national law in light of EU law.[16]

Similar to national legal orders, the EU legal order has its own catalogue of basic rights, namely the Charter of Fundamental Rights of the European Union (EUChFR) which has the same legal status as the Treaties (Article 6(1)(1) TEU). Besides traditionally recognized basic rights, the EUChFR, similar to the Swiss Federal Constitution, lays down fundamental rights specifically addressed to the "fields of medicine and biology" (Article 3(2) EUChFR). Importantly, the individual rights guaranteed under the EUChFR do not only bind EU organs but also the Member States whenever there is a situation governed by EU law (*cf.* Article 51(1) (1) EUChFR).[17] Accordingly, to the extent that somatic cell/gene therapies based on genome-edited iPSCs are regulated by Member States under, or on the basis of, EU law,[18] the EUChFR has to be taken into account by their administrative authorities and courts as well.

9.2.1.1.3 International Law

Furthermore, States are also bound by rules of public international law.[19] The sources of law most pertinent in the field of regenerative medicine are human rights treaties.[20] Of importance are also certain international soft law instruments.[21]

However, a human rights regime which is devoted specifically to so-called 'biomedicine' exists within Europe only. In 1997, the Biomedicine Convention

[16] CJEU, C-14/83, Von Colson und Kamann v Land Nordrhein-Westfalen, ECLI:EU:C:1984:153, para. 26.

[17] CJEU, C-609/17 and C-610/17, TSN, ECLI:EU:C:2019:981, paras. 46, 53.

[18] *Cf.* fn. 15.

[19] The most important sources of public international law are listed in Article 38(1)(a)–(c) Statute of the International Court of Justice: treaties, customary law and general principles of law.

[20] *E.g.*, International Covenant on Civil and Political Rights of 1966 (ICCPR) and International Covenant on Economic, Social and Cultural Rights of 1966 (ICESCR) to which all States under review are treaty parties (except for the United States which has signed but never ratified the ICESCR).

[21] *E.g.*, instruments passed by the World Medical Association, such as the Declaration of Helsinki—Ethical Principles for Medical Research involving Human Subjects of 1964, the Statement on Genetic Counseling and Genetic Engineering of 1987 and the Declaration of Reykjavik—Ethical Considerations Regarding the Use of Genetics in Health Care of 2005. Equally important are guidelines by the International Society for Stem Cell Research (ISSCR), *e.g.*, the ISSCR Guidelines for Stem Cell Research and Clinical Translation of 2021 and the Informed Consent Standard for Stem Cell-Based Interventions Offered Outside of Formal Clinical Trials of 2019.

(also known as the Oviedo Convention)[22] was adopted within the framework of the Council of Europe (CoE).[23] The CoE is an international organisation of its own which is separate from the EU[24] and whose membership amounts to 47 European States including all 27 Member States of the EU. Interestingly, not all European countries under review have become treaty parties to the Biomedicine Convention. In contrast to France and Switzerland, Germany has not ratified the Biomedicine Convention so far because, in certain respects,[25] it considered the Biomedicine Convention not to be sufficiently strict. Regarding genome-edited iPSC-based cell/gene therapies, several provisions of the Biomedicine Convention may be pertinent.[26] Some of these provisions are 'self-executing', *i.e.* directly applicable,[27] and, therefore, are to be applied by domestic public authorities and courts of the parties to the Convention.[28]

Of course, the European Convention of Human Rights (ECHR), including the related jurisprudence of the European Court of Human Rights (ECtHR), must not be overlooked.[29] The ECHR is the most important of all human rights treaties adopted within the framework of the CoE. Its provisions and the related ECtHR jurisprudence also guide the interpretation of the EUChFR (*cf.* Article 52(3)(1) EUChFR) and, as the case may be, the interpretation of national, including constitutional, law.[30] What is more, all human rights provisions of the ECHR are 'self-executing' and, thus, directly applicable within the domestic legal order of the treaty parties.

[22] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine of 1997.

[23] In the aftermath, four additional protocols have been adopted two of which are of particular significance here: Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin of 2002 and Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research of 2005.

[24] Which is an international organization as well but, due to the fact that the Member States have conferred real governmental powers upon the EU, it is specifically distinct from ordinary international organizations in that, on the basis of the attributed, albeit limited, governmental powers, it may act effectively, within the confines of the Treaties, like a State. Therefore, the CJEU held that the EU (then still the European Economic Community) "constitutes a new legal order of international law for the benefit of which the states have limited their sovereign rights, albeit within limited fields, and the subjects of which comprise not only Member States but also their nationals" (CJEU, C-26/62, Van Gend en Loos v Administratie der Belastingen, ECLI:EU:C:1963:1, ECR 1962, 1 (12)).

[25] As regards embryo research and research on human beings incapable of expressing informed consent (*cf.* Articles 6, 7, 17, 18 and 20 Biomedicine Convention). See Andorno (2005), p. 134.

[26] Especially on germ line therapy see Article 13, on scientific research involving human beings see Articles 15–17, on embryo research see Article 18, on tissue donation see Articles 19–22.

[27] On direct applicability of treaty norms see, *e.g.*, Klabbers (2021), pp. 327–331.

[28] Schweizer et al., Chap. 5, Sect. 5.2.1.2 (this volume).

[29] The same holds true, as regards the treatment of the patients' biological data, for the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data of 1981.

[30] *E.g.*, for Germany, see Federal Constitutional Court, Order of the Second Senate of 14 October 2004, 2 BvR 1481/04, paras. 32 and 62 (http://www.bverfg.de/e/rs20041014_2bvr148104en.html).

9.2.1.1.4 Federal Systems

Within the federations under review (Germany, Switzerland and the United States), the relevant statutes, secondary rules and guidelines are adopted on the federal level as regards somatic cell/gene therapies including those based on genome-edited iPSCs. This implies that the respective regulatory competences have been conferred upon the federal government.

The same applies within the EU which is a federal entity as well. Hence, to a highly significant extent, the French and German regulation of somatic cell/gene therapies based on genome-edited iPSCs is governed (through directly applicable Regulations), or determined (through Directives to be implemented by the Member States), by EU law.[31]

Accordingly, since genome-edited iPSC-based cell/gene therapies and, more generally, medicinal products are governed essentially by federal regulatory frameworks, one may conclude that the underlying policy choice is that even supply of such products should not be hampered by legal fragmentation resulting from divergent regulatory requirements on the state level or, within the EU, the Member State level.

9.2.1.2 Substantive Aspects

9.2.1.2.1 Medicinal Products Regulation

Regarding the substance of the law applicable to somatic cell/gene therapies based on genome-edited iPSCs, the statutes and any secondary rules belong, primarily, to the field of medicinal products law. In some jurisdictions, statutes have been specifically adopted to address high-tech, biotech or advanced medicinal products in particular. This applies to the EU[32] (and, accordingly, to the EU Member States France and Germany) as well as to Japan,[33] Korea[34] and the United States.[35]

[31] On France, see Mahalatchimy, Chap. 4, Sect. 4.2.1 (this volume); on Germany, see Frenken and Lüttge, Chap. 3, Sect. 3.2.2 (this volume).

[32] Biotech Medicinal Products Regulation (EC) No. 726/2004, ATMP Regulation (EC) No. 1394/2007. See, *e.g.*, Mahalatchimy, Chap. 4, Sect. 4.2.1 (this volume).

[33] Regenerative Medicine Promotion Act of 2013; Regenerative Medicine Safety Act of 2013. See Okura and Matsuyama, Chap. 7, Sect. 7.2.1 (this volume).

[34] Advanced Regenerative Medicine Act of 2019. See Shin, Chap. 8, Sect. 8.2 (this volume).

[35] 21st Century Cures Act of 2016. See Sanzo, Chap. 6, Sect. 6.2 (this volume).

9.2.1.2.2 GMO Regulation

In the EU, peculiar regulatory problems may arise from the fact that genome editing[36] is a method of genetic modification of organisms and, therefore, results in genetically modified organisms (GMOs) within the meaning of the law.[37] In fact, it follows from the CJEU's judgement of July 25, 2018,[38] that genome-edited organisms are GMOs and, as such, subject to the EU's regulatory framework for GMOs. Although this judgment directly relates to EU legislation governing the deliberate release of GMOs into the environment only,[39] its reasoning and conclusions are considered to be applicable to EU legislation on the contained use of GMOs[40] as well. Accordingly, *e.g.*, the generation and use of genome-edited cells, *e.g.*, in laboratories and hospitals is, in principle, subject to the legal rules on the contained use of GMOs.

This leads to a complex interplay between medicinal products law and GMO law, especially on the domestic level of the EU Member States.[41] Indeed, the EU legislature has only very recently acknowledged that "[e]xperience shows that, in clinical trials with investigational medicinal products containing or consisting of GMOs, the procedure to achieve compliance with the requirements of Directives 2001/18/EC and 2009/41/EC as regards the environmental risk assessment and consent by the competent authority of a Member State is complex and can take a significant amount of time".[42]

[36] The genome editing techniques are either oligonucleotide mutagenesis (ODM) or site-directed nuclease (SDN) techniques using Zinc finger nucleases, TALENs or CRISPR/Cas. On these techniques see, *e.g.*, European Commission (2017), pp. 56–60.

[37] Contrary to the EU which developed a 'process-based' legal framework for GMOs, *i.e.* a 'horizontal' framework for all organisms resulting from the use of certain genetic engineering techniques, the United States opted for a 'product-based' approach applying existing product-related laws and regulations such as the Federal Food, Drug, and Cosmetic Act (FFDCA) to innovative products independent of the technique used for their development. See Sanzo, Chap. 6, Sect. 6.2 (this volume). See also the 'Coordinated Framework for Regulation of Biotechnology' of 1986 (Federal Register 51 [1986], p. 23302).

[38] CJEU, C-528/16, Confédération paysanne and Others, ECLI:EU:C:2018:583, paras. 51, 47, 23.

[39] Since it concerned the interpretation of the GMO definition (Article 2(2)) and the exemption clause (Article 3(1)) laid down in Directive 2001/18/EC on the deliberate release into the environment of GMOs.

[40] Directive 2009/41/EC on the contained use of genetically modified micro-organisms (GMMs).

[41] See *infra* Sects. 9.3.4 and 9.4.4. Similarly in Switzerland. See Schweizer et al., Chap. 5, Sect. 5.3.3 (this volume); Dederer and Frenken (2021), pp. 20–22 and 36–37.

[42] Recital 8 of Regulation (EU) 2020/1043 on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease (COVID-19).

9.2.1.2.3 Bioethics Regulation

As regards germ line therapy, most countries under review have enacted statutory provisions which prohibit inheritable genetic modifications of the germ line.[43] Such rules on heritable germ line interventions are often part of statutes which cover several other issues of bioethics, *e.g.*, embryo protection, embryonic stem cell research, research involving human beings, in-vitro fertilization, cloning, genetic diagnoses, biobanks, etc.[44]

9.2.1.2.4 Personal Data Protection Regulation

Biological data of patients are personal data. Therefore, the use of biological data, *e.g.*, of patients in the course of clinical trials, raises the issue of personal data protection. The pertinent legal rules may be laid down in general data protection laws[45] or in laws which specifically apply, *inter alia*, to health or genetic data[46] or in the laws related to medicinal products or bioethics.[47] In addition, since data protection is an expression of a person's autonomy, relevant provisions may have been also incorporated into constitutions, typically taking the form of fundamental rights.[48]

9.2.2 Competent Authorities

The competent authorities charged with the implementation and enforcement of rules applicable to somatic cell/gene therapies based on genome-edited iPSCs are, typically, centralized public authorities (be they ministries[49] or regulatory agencies[50]). This implies that, within the federations under review (Germany, Switzerland and the United States), the competent authorities are federal regulatory

[43] See *infra* Sect. 9.7. Switzerland has incorporated the prohibition of heritable germ line modifications also into its Federal Constitution (Article 119(2)(a)). See Schweizer et al., Chap. 5, Sect. 5.4.3.1 (this volume).

[44] CH: Reproductive Medicine Act, Stem Cell Research Act; D: Embryo Protection Act, Stem Cell Act; F: Bioethics Law; ROK: Bioethics Act.

[45] CH: Federal Act on Data Protection; EU: General Data Protection Regulation (EU) 2016/679; F: Law no. 78-17 on information technology, files and freedoms; ROK: Personal Information Protection Act.

[46] CH: Federal Act on Human Genetic Testing; USA: Health Insurance Portability and Accountability Act of 1996, Genetic Information Nondiscrimination Act of 2008.

[47] CH: Human Research Act; F: Public Health Code; ROK: Advanced Regenerative Medicine Act, Bioethics Act.

[48] For details see *infra* Sect. 9.6.

[49] J: Ministry of Health, Labour and Welfare (MHLW); ROK: Ministry of Food and Drug Safety.

[50] F: Agence nationale de sécurité du médicament et des produits de santé (ANSM).

agencies.[51] To a certain extent, this holds true for the EU again which is a federal entity as well. With regard to the placing on the market of so-called 'advanced therapy medicinal products' (ATMPs), and, hence, of genome-edited iPSC-based cell/gene therapy products,[52] it is the European Commission which grants the marketing authorization on the basis of the scientific opinion by EMA.[53]

Regarding clinical trials, committees or commissions charged with the ethical evaluation of the proposed investigations are involved. The express consent of these bodies is, typically, an indispensable prerequisite for clinical trials. In general,[54] these committees or commissions are not centralized bodies but have been established on the local level, *i.e.*, usually, within the respective institutions (*e.g.*, universities, hospitals),[55] or on the regional level.[56]

In addition, in all countries under review with the notable exception of the United States,[57] the manufacturing of (investigational) regenerative medicinal products (such as the genome-edited iPSC-based somatic cell/gene therapy products at hand) requires a manufacturing licence. In most countries, the task of granting these licences has been assigned to those public authorities which are also in charge of issuing the prior authorization, or reviewing the prior notification, of the (investigational) medicinal product.[58] It is only within Germany that manufacturing licences are to be accorded by regional authorities of the states ('Länder') and not by the PEI, *i.e.* the federal regulatory agency competent for ATMPs.[59] This is due to the distribution of powers within Germany's federal system of government.

Moreover, as has been outlined *supra*, EU Member States, *e.g.*, France and Germany, have to adhere to the legal framework for GMOs as well.[60] The same applies to Switzerland.[61] As a consequence, some more public authorities come into play. As regards, *e.g.*, clinical trials related to genome-edited iPSC-based somatic

[51] CH: Swiss Agency for Therapeutic Products (Swissmedic); D: Paul-Ehrlich-Institut (PEI): Federal Institute for Vaccines and Biomedicines; USA: Food and Drug Administration (FDA).

[52] See Mahalatchimy, Chap. 4, Sect. 4.3 (this volume); Frenken and Lüttge, Chap. 3, Sect. 3.2.4 (this volume).

[53] See, *e.g.*, Mahalatchimy, Chap. 4, Sect. 4.2.2 (this volume).

[54] With the exception of Korea where the required ethical review is conducted by the National Regenerative Medical Review Committee. See Shin, Chap. 8, Sect. 8.3.2.4 (this volume).

[55] As in Germany (Ethics Committees), Japan (Special Certified Regenerative Medicine Committees) and the United States (Institutional Review Boards).

[56] As in France (regional 'Comités de Protection des Personnes') and Switzerland (Cantonal Ethics Commissions). In Germany, some Ethics Committees have been also established by the states ('Länder') or by their Medical Chambers which are administrative bodies of professional self-government.

[57] See *infra* Sects. 9.3.3 and 9.4.3.

[58] CH: Swissmedic; F: ANSM; J: MHLW; ROK: Ministry of Food and Drug Safety.

[59] Frenken and Lüttge, Chap. 3, Sect. 3.2.1 (this volume).

[60] On France, see Mahalatchimy, Chap. 4, Sects. 4.1, 4.2.1, 4.2.2, 4.3.2.1, 4.3.3 (this volume); on Germany, see Frenken and Lüttge, Chap. 3, Sects. 3.2.1, 3.2.5, 3.3.3.1, 3.3.3.3, 3.3.4.2, 3.3.4.4 (this volume).

[61] See Schweizer et al., Chap. 5, Sect. 5.3.3 (this volume); Dederer and Frenken (2021), pp. 20–22 and 36–37.

cell/gene therapy products, which contain or consist of GMOs, specialized regulatory agencies or scientific advisory bodies have to be involved in the prior authorization procedure.[62] As regards the manufacturing of the GMOs, still other public authorities may be responsible as regards implementation and enforcement of the relevant rules on the contained use of GMOs.[63]

9.3 Clinical Trials

9.3.1 In Advance Control Mechanisms

The in advance control mechanisms regarding clinical trials of genome-edited iPSC-based cell/gene therapies are, very generally speaking, similar in all countries under review. In principle, the respective control mechanism has two tracks. One track concerns the safety of the investigational medicinal product or the clinical investigation respectively, the other track concerns the risk-benefit ratio from an ethical perspective. The assessment of the safety of the investigational medicinal products or the clinical investigation respectively is carried out by a public administrative authority in all countries reviewed. The conduct of the ethical risk-benefit assessment, on the other hand, falls within the remit of committees or commissions which are not necessarily established by the central or a regional government but, as the case may be, by the relevant private or state institutions which the sponsors or investigators belong to.[64]

Regarding the evaluation of the safety of the investigational medicinal product or the clinical investigation respectively, two different in advance review mechanisms may be distinguished: prior authorization (*infra* Sect. 9.3.1.1) and prior notification (*infra* Sect. 9.3.1.2).

9.3.1.1 Prior Authorization

The mechanism of prior authorization means that the clinical trial may commence only upon express consent by the competent body. Such consent is granted through the instrument of an authorization. The authorization, first, asserts that the clinical trial is in conformity with all pertinent legal requirements and, second, gives clearance for the clinical trial to start. The concept of prior authorization implies

[62] CH: Federal Office for the Environment (FOEN), Swiss Expert Committee for Biosafety (SECB), Federal Office of Public Health (FOPH); D: Federal Office of Consumer Protection and Food Safety; F: Ministry of Research, Ministry of the Environment, High Council of Biotechnologies (HCB).

[63] *E.g.*, in Germany, implementation and enforcement of the contained use regime falls within the competence of regional administrative authorities of the states ('Länder'). Frenken and Lüttge, Chap. 3, Sect. 3.2.1 (this volume).

[64] See *supra* Sect. 9.2.2.

that, without valid authorization, the clinical trial may not be carried out even if the time limit for review by the competent administrative authority has expired. With the exception of Japan and the United States,[65] all other countries under review have adopted the prior authorization approach.

9.3.1.2 Prior Notification

In contrast, the mechanism of prior notification means that the clinical trial may commence after it has been notified to the competent authority. Usually, however, the investigator may begin the clinical trial only after a certain waiting period has expired. This implies that the start of the clinical trial does not depend on express consent by the relevant administrative authority. Regarding the countries under review, the instrument of prior notification has been adopted by Japan[66] and the United States[67] only. If FDA (in the United States) or MHLW (in Japan) has not interdicted the clinical trial, the investigator may go for the clinical trial after expiry of the waiting period. At least in the United States, the clinical investigation may start at an even earlier point of time if FDA notifies the sponsor accordingly.[68]

9.3.2 Time Limits for Review

Notwithstanding the regulatory approach (*i.e.* prior authorization or prior notification),[69] the competent administrative authority is always assigned a certain period of time for the purpose of evaluating the application for authorization or the notification. The respective time limits vary considerably. In the EU and, therefore, in France[70] and Germany,[71] the timeline for authorizing clinical trials with ATMPs is, currently, 90 days. Other jurisdictions under review allot much shorter time frames, *e.g.*, 60 days in Switzerland[72] and only 30 days in Japan[73] and the United States.[74]

The number of days of the relevant timelines for administrative review is, in itself, of limited significance, though. Rather, what matters is whether the competent public authorities really meet the time limits in practice. In the United States, *e.g.*, FDA

[65] See *infra* Sect. 9.3.1.2.
[66] Maeda et al. (2015), p. 154.
[67] Sanzo, Chap. 6, Sect. 6.2 (this volume); also Bailey et al. (2015), p. 9.
[68] 21 CFR 312.40(b)(2).
[69] *Cf. supra* Sect. 9.3.1.
[70] Mahalatchimy, Chap. 4, Sect. 4.3.3 (this volume).
[71] Frenken and Lüttge, Chap. 3, Sect. 3.3.3.3 (this volume).
[72] Marti (2015), p. 132.
[73] Maeda et al. (2015), p. 154.
[74] Bailey et al. (2015), p. 9.

seems, indeed, to be able to review the notified clinical trials within the extremely short period of only 30 days.[75] An additional point to consider is that administrative authorities may 'stop the clock' by requesting additional information from the investigator or sponsor. Accordingly, in practice, the actual administrative in advance control may take much longer than one might envisage by looking just at the formal timeline specified in the law.

9.3.3 Manufacturing Requirements

The investigational medicinal product needs to be manufactured in order to be applied to subjects in the course of the clinical trial. Usually, manufacturing the investigational medicinal product requires a manufacturing licence. This licence constitutes a kind of prior authorization because manufacturing may start only upon receipt of the licence. With the exception of the United States, all countries under review have opted for the requirement of a manufacturing licence. In the United States, FDA does neither require that investigators or sponsors submit a manufacturing licence nor issue such a licence.[76] Rather, FDA asks sponsors for, and then reviews, so-called "CMC"[77] information only.[78]

In all countries under review, with the exception of Germany, the competence to issue the manufacturing licence lies with the same public authority which grants the clinical trial authorization. Hence, in Germany,[79] as the case may be, sponsors may have to approach two different administrative authorities, *i.e.* the Paul-Ehrlich-Institut (PEI) as regards the prior authorization of the clinical trial and the competent regional authority within the state ('Land') concerned as regards the licence for manufacturing of the investigational medicinal product.

9.3.4 GMO-Specific Requirements

Further bureaucratic obstacles may stem from regulation that applies specifically in regard to genetically modified organisms (GMOs). Such GMO-specific regulation has been adopted by the EU and, hence, had to be implemented by the EU Member States such as, *e.g.*, France and Germany. Their relevant legal frameworks on GMOs apply, in principle, also to genome-edited iPSC-based cell/gene therapies, since, in

[75] Dederer and Frenken (2021), pp. 24 and 88–89.

[76] Dederer and Frenken (2021), pp. 23 and 89–90.

[77] Chemistry, Manufacturing, and Control.

[78] Sanzo, Chap. 6, Sects. 6.2 and 6.2.3 (this volume). Regarding somatic cell/gene therapy products based on genome-edited iPSCs see, especially, FDA (2020).

[79] See *supra* Sect. 9.2.2.

light of the aforementioned judgment of the CJEU of July 25, 2018,[80] the genome-edited cells constitute GMOs, or GMMs[81] respectively, within the meaning of EU law.

As has been mentioned before,[82] the EU legislature has realized that "[e]xperience shows that, in clinical trials with investigational medicinal products containing or consisting of GMOs, the procedure to achieve compliance with the requirements of Directives 2001/18/EC and 2009/41/EC as regards the environmental risk assessment and consent by the competent authority of a Member State is complex and can take a significant amount of time".[83] Indeed, sponsors not only must comply with another regulatory framework, *i.e.* the GMO framework, but, as the case may be, they have to turn to yet other administrative authorities as well.[84]

The rules laid down in the aforementioned Directives 2001/18/EC (on the deliberate release of GMOs into the environment) and 2009/41/EC (on the contained use of GMMs) have to be implemented by the EU Member States on the national level.[85] In practice, Member States have implemented the relevant rules differently, especially as regards clinical trials involving investigational medicinal products containing or consisting of GMOs. Accordingly, this regulatory patchwork affects genome-edited iPSC-based somatic cell/gene therapies, too. Indeed, the EU legislature has candidly acknowledged the problems resulting from such non-uniform implementation only very recently:

> national requirements and procedures for the environmental risk assessment and written consent by competent authorities for the deliberate release of GMOs under Directive 2001/18/EC vary greatly from one Member State to another. Whereas in some Member States a single request for authorisation concerning the conduct of the clinical trial and the GMO aspects can be submitted to a single competent authority, in other Member States parallel requests need to be submitted to different competent authorities. Furthermore, some Member States apply Directive 2001/18/EC, others apply Directive 2009/41/EC and there are Member States that apply either Directive 2009/41/EC or 2001/18/EC depending on the specific circumstances of a clinical trial, so it is not possible to determine a priori the national procedure that is to be followed. Other Member States apply both Directives simultaneously to different operations within the same clinical trial. Attempts to streamline the process through informal coordination between Member States' competent authorities have been

[80] See *supra* in fn. 38.

[81] Genetically Modified Micro-organisms. While Directive 2001/18/EC on the deliberate release into the environment applies to all GMOs (*i.e.* including genetically modified micro-organisms), Directive 2009/41/EC on the contained use applies to GMMs only. The term 'micro-organism' is defined as "any microbiological entity, cellular or non-cellular, . . ., including . . . animal and plant cells in culture" (Article 2(a) Directive 2009/41/EC). Since the list of examples is not exhaustive ("including"), human cells constitute micro-organisms within the meaning of Directive 2009/41/EC as well. It is of note that most EU Member States, including both France and Germany, have permissibly extended the scope of application of their domestic contained use regime beyond micro-organisms to all kinds of organisms.

[82] See *supra* Sect. 9.2.1.2.

[83] Recital 8 of Regulation (EU) 2020/1043.

[84] See *supra* Sect. 9.2.2.

[85] See also *supra* Sect. 9.2.1.1.

unsuccessful. There are also variations between national requirements as to the content of the technical dossier.[86]

This regulatory fragmentation within the EU can be exemplified by looking at France and Germany. In France, the contained use regime (*cf.* Directive 2009/41/EC) applies in any case.[87] This means that, on the basis of French GMO legislation, the Ministry of Research as well as the High Council of Biotechnologies (HCB) get involved.[88] In addition, where appropriate, the deliberate release regime (*cf.* Directive 2001/18/EC) may come into play if the GMOs administered to the subjects might be released into the environment.[89] In the case at hand, *i.e.* in the case of somatic cell/gene therapies based on genome-edited iPSCs, however, the deliberate release regime seems not to be applicable because the genome-edited cells are implanted, or injected, into the subjects and are, henceforth, forming an integral part of their body. What is more, human beings as such, and therefore the subjects of the clinical trials, are, by definition (*cf.* Article 2(2) Directive 2001/18/EC), not GMOs within the meaning of Directive 2001/18/EC on the deliberate release into the environment. Accordingly, if, after treatment with genome-edited cells within the context of an *ex vivo* somatic cell/gene therapy based on genome-edited iPSCs, subjects leave the clinic, the subjects themselves are not GMOs released into the environment.

In contrast, Germany made use of the "single entry point"-concept according to which the authorization of the clinical trial issued by the Paul-Ehrlich-Institut (PEI) under the Medicinal Products Act includes the deliberate release authorization under the German Genetic Engineering Act. For that purpose, the PEI has to consult with the Federal Office of Consumer Protection and Food Safety (BVL) which is, in accordance with the Genetic Engineering Act, the competent authority as regards deliberate release and placing on the market of GMOs. As a result, pursuant to the rules of the Genetic Engineering Act, the contained use regime is not applicable any longer (except for the generation of the relevant GMOs) which means that the use of GMOs in clinical trials authorized by the PEI (*e.g.*, storage, transport and, especially, administration of the GMOs to the subjects) is not governed by the contained use regulations.[90]

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[86] Recital 9 of Regulation (EU) 2020/1043.

[87] According to the contained use regime, the generation and any use (*e.g.*, storage, transport, application, destruction, disposal; *cf.* Article 2(c) Directive 2009/41/EC) of GMMs, *e.g.*, in laboratories or hospitals has to be carried out in conformity with certain containment measures to be taken in accordance with the risk level of the respective activity (Article 5(1) Directive 2009/41/EC). Such containment measures might be applicable to the subjects of clinical trials after their treatment with, *e.g.*, *ex vivo* cell/gene therapy products for a certain period of time as well. See, with a view to France, Mahalatchimy, Chap. 4, Sect. 4.3.3 (this volume).

[88] Mahalatchimy, Chap. 4, Sect. 4.3.3 (this volume).

[89] *E.g.*, if the investigational gene therapy medicinal product is a genetically modified virus to be inhaled by the subjects using an aerosol spray. See Dederer and Frenken (2021), pp. 13–14.

[90] Dederer and Frenken (2021), p. 5. This follows from the German legal definition of 'contained use activities'. An activity does not constitute a contained use activity to be carried out in

The legal situation in Switzerland is similar to the German situation. Switzerland also follows the "one door, one key"-approach. Accordingly, Swissmedic grants the authorization of the clinical trial involving GMOs on the basis of an assessment of the risks to human health and the environment resulting from the relevant GMO. For that purpose, Swissmedic has to ask three federal administrative authorities in charge of implementing the Swiss GMO regulations for consent.[91]

The fact that other countries do not possess a regulatory framework addressed specifically to GMOs does not necessarily imply that, *e.g.*, environmental risks arising from gene therapies are not taken into account. Indeed, *e.g.*, in the United States, the National Environment Policy Act (NEPA) of 1969 requires all federal agencies to assess the environmental impacts of their measures. This applies to FDA and, hence, to the regulation of clinical trials under the Federal Food, Drug, and Cosmetic Act (FFDCA) as well.[92] However, FDA has exempted clinical trials from the requirement that sponsors have to submit an environmental assessment (EA). The reasoning behind this policy is that clinical trials are subject to strict administrative oversight and concern a limited group of persons only.[93]

9.3.5 Consultation Mechanisms

Somatic cell/gene therapies, especially *ex vivo* therapies based, *e.g.*, on genome-edited iPSCs, involve highly innovative medicinal products which differ significantly from biopharmaceuticals (*e.g.*, proteins produced by means of genetically modified bacteria) or small molecule drugs.[94] Therefore, sponsors or investigators are usually strongly encouraged to consult as early as possible with the competent authorities in order to get advice. Such advice relates, *inter alia*, to manufacturing requirements, preclinical studies, the different, especially early, phases of the envisaged clinical trials as well as data and information requirements. If certain medicinal products qualify for special procedures,[95] sponsors or investigators may get particularly intense guidance and comprehensive advisory services from the competent authorities.

Although such (often informal) consultations, discussions or meetings seem to be commonplace in all jurisdictions, at least some of them have introduced special programmes. *E.g.*, in the United States, besides regular pre-IND meetings, FDA

installations under containment measures if the GMO or GMM has been authorized for the deliberate release into the environment or for placing on the market (*cf.* Section 3(2)(b) Genetic Engineering Act).

[91] Dederer and Frenken (2021), p. 22.

[92] See also Dederer and Frenken (2021), p. 25.

[93] FDA (2015), p. 4.

[94] See, *e.g.*, Sanzo, Chap. 6, Sect. 6.2.2 (this volume).

[95] See *infra* Sect. 9.4.2.1.

offers advice through its INTERACT[96] programme and, most recently, its newly established 'CATT'[97] programme. In Japan, sponsors or investigators are encouraged to enter into 'regulatory scientific strategic consultations'[98] which should follow a particular order starting with quality consultations and continuing with non-clinical safety consultations and, then, clinical trial protocol consultations.

9.3.6 Country-Specific Peculiarities

This subsection highlights a few country-specific requirements identified in the country reports of this volume. The following collection of country-specific observations should not be considered to be exhaustive.

9.3.6.1 Japan

In Japan, one has to distinguish 'clinical trials' from 'clinical research'. The conduct of 'clinical trials' is, like in all other countries under review, an indispensable prerequisite if the (investigational) medicinal product is intended to be placed on the market on the basis of a marketing authorization. In contrast, 'clinical research' is carried out for purposes of scientific research only.[99] Accordingly, different rules apply. This holds, especially, true for genome-edited iPSC-based somatic cell/gene therapies. 'Clinical trials' of such *ex vivo* cell/gene therapies are governed by the Pharmaceuticals and Medical Devices Act (PMD Act) whereas 'clinical research' on such therapies is subject to the provisions of the Regenerative Medicine Safety Act (RMS Act).[100]

Under the RMS Act, clinical research on regenerative medicines is classified into three categories (Type 1-3) depending on the possible risks to life and health associated with the particular product. Type 1 regenerative medicines are high-risk products whereas Type 2 regenerative medicines are medium-risk products and Type 3 regenerative medicines are low-risk products.[101] According to the classification scheme,[102] classification depends, *inter alia*, on the cellular source (*e.g.*, human embryonic stem cells, human iPSCs; animal or allogeneic cells; etc.), the

[96] Initial Targeted Engagement for Regulatory Advice on CBER Products.

[97] CBER Advanced Technology Team.

[98] Okura and Matsuyama, Chap. 7, Sect. 7.2.4.3 (this volume).

[99] Maeda et al. (2015), pp. 151, 153.

[100] See the figure by Maeda et al. (2015), p. 152; see also Okura and Matsuyama, Chap. 7, Sect. 7.2.5.1 (this volume), on the origins of the RMS Act which can be traced back to the former MHLW 'Directives for Human Stem Cell-based Clinical Research'.

[101] Okura and Matsuyama, Chap. 7, Sect. 7.2.5.2 (this volume).

[102] See the flowchart by Okura and Matsuyama, Chap. 7, Sect. 7.2.5.2 (this volume).

modification through genetic engineering techniques and the kind of use (*e.g.*, homologous). On the basis of these criteria, somatic cell/gene therapies based on genome-edited iPSCs belong to Type 1 regenerative medicines.[103] The significance of this risk-based typology is that the intensity of in advance control varies depending on the type of regenerative medicines.[104] In case of Type 1 products, researchers have to submit their research plan to the competent Special Certified Regenerative Medicine Committee. The committee's opinion has to be taken into account for the purpose of the subsequent submission of the research plan to MHLW. The Ministry, in turn, consults with the Health Science Council. The regenerative medicine product may be administered in the course of the clinical research after expiry of a waiting period of 90 days. This administrative procedure has been characterised as a being "effectively . . . a permission-based scheme".[105]

9.3.6.2 Korea

In Korea, clinics which intend to conduct clinical trials of gene therapies, or gene therapy medicinal products respectively, have to be certified as so-called 'advanced regenerative medicine clinics' by the Korean Ministry of Health. This applies, in particular, to clinical trials of genome-edited iPSC-based somatic cell/gene therapies which may be performed in such specially certified institutions only.[106]

Another interesting feature of the Korean regulatory framework is that clinical trials of gene therapies, or gene therapy medicinal products respectively, are classified into three categories depending on the risks involved. Class A-trials comprise high-risk clinical investigations, whereas Class B-trials encompass medium-risk investigations and Class C-trials low-risk investigations.[107] The classification is of importance with a view to the acquisition of the cells administered in the course of the clinical trials. In case of Class A- and Class B-trials, the cells have to be acquired from an institute which is specialized in the treatment of cells intended for advanced regenerative medicine uses and which will be newly established on the basis of the Advanced Regenerative Medicine Act of 2019.[108]

Furthermore, in contrast to the other countries reviewed, the Korean legislation restricted both *in vivo* and *ex vivo* gene therapies explicitly to certain indications for

[103] Okura and Matsuyama, Chap. 7, Sect. 7.2.5.2 (this volume).

[104] See Okura and Matsuyama, Chap. 7, Sect. 7.2.5.2 (this volume).

[105] Okura and Matsuyama, Chap. 7, Sect. 7.2.5.2 (this volume).

[106] Shin, Chap. 8, Sect. 8.3.2.4 (this volume).

[107] Shin, Chap. 8, Sect. 8.3.2.4 (this volume).

[108] Shin, Chap. 8, Sect. 8.3.2.4 (this volume). In Switzerland, clinical trials are also classified into three categories (Category A–C). However, unlike in Japan (*supra* Sect. 9.3.6.1) and Korea, this classification is not specifically related to regenerative medicine products or cell/gene therapy medicinal products respectively. The Swiss classification is decisive for the intensity of in advance review of clinical trials and for liability coverages. See Schweizer et al., Chap. 5, Sects. 5.3.2.3 and 5.3.2.4 (this volume).

ethical reasons. According to Korea's Bioethics Law, research on gene therapies, and, therefore, also on genome-edited iPSC-based cell/gene therapies, is permitted only with a view to certain kinds of diseases or to diseases hitherto untreatable or only unsatisfactorily treatable.[109]

9.4 Placing on the Market

9.4.1 Pre-Marketing Control Mechanisms

The placing on the market of somatic cell/gene therapy products based on genome-edited iPSCs is subject to prior authorization in all countries under review. This means that, unless an administrative authority has given express consent, the medicinal product must not be placed on the market. The competent authority grants the authorization if the cell/gene therapy product at issue meets the required safety, quality and efficacy standards.

9.4.2 Special Procedures

All countries reviewed have special authorization procedures in place. In some countries under review, *e.g.*, in Japan[110] and the United States,[111] special procedures have been established specifically with a view to regenerative medicine products.

Very broadly speaking, the purpose of such special procedures is to facilitate market access for medicinal products which are intended, *e.g.*, for patients who suffer from life-threatening or other serious diseases or for the treatment of infectious diseases, or which belong to a particular category of highly innovative products such as, *e.g.*, regenerative medicine products. Additional requirements (*e.g.*, an unmet medical need, a substantial improvement compared to currently available treatments) may need to be met as well in order to benefit from such special authorization procedures.

The special procedures available in the countries under review can be grouped in three categories: procedures in the course of which sponsors and investigators get special attention (*infra* Sect. 9.4.2.1), procedures which allow for accelerated review (*infra* Sect. 9.4.2.2), and procedures which simplify the data submission exigencies (*infra* Sect. 9.4.2.3).[112] These three categories of special procedures are not strictly separated, *i.e.* two or more special procedures may be combinable depending on the

[109] Shin, Chap. 8, Sect. 8.3.2.4 (this volume).

[110] Okura and Matsuyama, Chap. 7, Sect. 7.2.4.2 (this volume).

[111] Sanzo, Chap. 6, Sect. 6.2.4.4 (this volume).

[112] Regarding this categorization see Dederer and Frenken (2021), pp. 94–95.

circumstances of the individual case,[113] or one and the same special procedure may combine several of the aforementioned special features (*i.e.* special attention, expedited review and simplified data requirements).

A recurring, albeit not always available,[114] feature of special procedures is the so-called 'rolling review'.[115] The concept behind 'rolling review' is that data collected during ongoing clinical trials may be submitted immediately to the competent authority for the purpose of review as soon as the data has become available, *i.e.* well before submission of a complete application for authorization of the medicinal product. As soon as the competent authority considers the data submitted to be sufficient, the sponsor may file the application for marketing authorization.

9.4.2.1 Intense Mentoring

The first category of special procedures may be called 'intense mentoring procedures'. This means that the communication and interaction between the competent authority and sponsors or investigators is particularly intense. Accordingly, the sponsors or investigators may benefit, *e.g.*, from more frequent consultations or more elaborate advice.

These intense mentoring procedures have different and unique denominations. *E.g.*, in the United States, three programmes come under the ambit of this kind of special procedures: the 'Fast Track' programme, the 'Breakthrough Therapy' programme and the 'Regenerative Medicine Advanced Therapy' (RMAT)[116] programme.[117] The importance of these programmes is that sponsors and investigators may benefit from FDA's consultation and advice services already at the clinical trials stage.[118] In the EU, it is the 'PRIME' ('Priority Medicines') programme which ensures close support throughout the product development process.[119]

[113] *E.g.*, in the United States, regarding a particular genome-edited iPSC-based cell/gene therapy product, sponsors might make use of the 'Regenerative Medicine Advanced Therapy', the 'Accelerated Approval' and the 'Breakthrough Therapy' programme at the same time. See Sanzo, Chap. 6, Sect. 6.2.4.4 (this volume).

[114] *E.g.*, in the EU, 'rolling review' seems to be applied only on an *ad hoc* basis in situations of public health emergencies such as a pandemic. See EMA (2020).

[115] On the United States see Sanzo, Chap. 6, Sect. 6.1.2 (this volume); on Korea *cf.* Moon-hee (2019); *cf.* also Dederer and Frenken (2021), pp. 34, 41–42, 45, 94–95.

[116] Which seems to be most pertinent as regards genome-edited iPSC-based somatic cell/gene therapies (Sanzo, Chap. 6, Sect. 6.2.4.4, this volume).

[117] On these programmes Sanzo, Chap. 6, Sects. 6.2.4.1–6.2.4.4 (this volume).

[118] *Cf.* Sanzo, Chap. 6, Sects. 6.2.4 and 6.2.4.4 (this volume).

[119] On PRIME see Dederer and Frenken (2021), pp. 35, 85, 103.

9.4.2.2 Accelerated Review

The second category of special procedures are 'accelerated review procedures'. Their essential feature is that time-limits for review by the competent authority are significantly reduced. *E.g.*, in the EU, the regular time frame of 210 days, during which the Committee for Medicinal Products for Human Use (CHMP)[120] of EMA has to prepare its scientific opinion, is lowered to a mere 150 days.[121] In the United States, under the 'Priority Review' programme, the FDA has to decide on a Biologics Licence Application (BLA) not within the regular timeline of 10 months, but within a shorter timeline of 6 months.[122] An extremely expedited review may take place in Korea in accordance with its recently adopted Advanced Regenerative Medicine Act of 2019. Pursuant to that act, the Ministry of Food and Drug Safety has to decide on the application for marketing authorization within a period of only 60 days.[123]

9.4.2.3 Provisional Authorization

Another concept for pushing on the review is to decrease the burden associated with the submission of evidence related to safety, quality and efficacy of the medicinal product. *E.g.*, under the 'Accelerated Approval' programme of the United States, the BLA applicant may demonstrate safety, quality and efficacy of the biologic with regard to so-called intermediate or surrogate endpoints only.[124] In contrast to regular endpoints, such intermediate or surrogate endpoints do not directly demonstrate a clinical benefit but rather simply allow for anticipating that, with a certain likelihood, the product will exhibit a particular clinical benefit. It goes without saying that the licence holder has to confirm the envisaged effects through the conduct of additional clinical trials.[125] Therefore, despite its name, the 'Accelerated Approval' programme does, strictly speaking, not belong to the 'accelerated review procedures' (*supra* Sect. 9.4.2.2) but, in fact, rather to those special procedures which provide for provisional authorizations. Of course, the alleviated requirements for the provisional substantiation of safety, quality and efficacy result, in the end, in an expedited review.

The special feature of the third category of special procedures, *i.e.* procedures aiming at provisional authorizations, is that, broadly speaking, marketing authorizations are granted on the basis of clinical data which is still incomplete in that it does not provide comprehensive and conclusive direct evidence of a certain clinical

[120] On the basis of a draft opinion by the Committee for Advanced Therapies (CAT).

[121] Frenken and Lüttge, Chap. 3, Sect. 3.3.3.2 (this volume); Dederer and Frenken (2021), pp. 33–34.

[122] Dederer and Frenken (2021), p. 42.

[123] Shin, Chap. 8, Sect. 8.3.2.5 (this volume).

[124] Sanzo, Chap. 6, Sect. 6.2.4.1 (this volume).

[125] FDA (2014), pp. 22–23.

benefit. In the EU, Switzerland and the United States, the application for a provisional authorization is not directly linked to the completion of a particular phase of the clinical trials. In contrast, *e.g.*, in Japan, phase II trials have to be completed before application for a provisional authorization.[126]

The authorization is provisional in that the data basis has to be completed by the sponsor through ongoing confirmatory clinical trials after the authorization has been issued. As a consequence, the competent authority restricts, or may have to restrict, provisional authorizations to a specified period of time of, *e.g.*, 1 year (in the EU, albeit on a renewable basis), a maximum of 2 years (in Switzerland) or even 7 years (in Japan).[127]

Furthermore, in general, provisional authorizations are issued on a conditional basis only. The most important condition is the aforementioned obligation of the sponsor to complete ongoing, or to commence additional, clinical trials for the purpose of generating a (more) complete data basis confirming the anticipated clinical benefits. Another condition may be, *e.g.*, in Japan, that only specialized physicians are allowed to apply the cell/gene therapy product.[128]

9.4.3 Manufacturing Requirements

Except for the United States,[129] an additional requirement for the placing on the market of somatic cell/gene therapy products is that their manufacturing requires a manufacturing licence issued by a public authority. This licence, first, ascertains that the manufacturing requirements are met and, second, clears the start of the manufacturing process. The most important manufacturing requirement is that the manufacturing process conforms to GMP[130] standards.

It is particularly noteworthy that most jurisdictions reviewed have developed either special GMP standards related specifically to regenerative medicinal products or, at least, special guidance notes. *E.g.*, Japan has introduced its own GMP standard called 'Good Gene, Cellular, and Tissue-based Manufacturing Practice' (GCTP).[131] The EU, *e.g.*, has also taken account of the fact that the manufacturing of ATMPs poses unique challenges specifically distinct from those associated with, *e.g.*, biopharmaceuticals or small molecule drugs. Hence, the European Commission has issued guidelines on 'Good Manufacturing Practice for Advanced Therapy

[126] *Cf.* Dederer and Frenken (2021), p. 43.

[127] *Cf.* Dederer and Frenken (2021), p. 44. Especially on Japan see also Okura and Matsuyama, Chap. 7, Sects. 7.2.1, 7.2.4.1, 7.2.4.2 (this volume).

[128] van Schothorst et al. (2016), p. 89.

[129] *Cf.* also *supra* Sect. 9.3.3.

[130] Good Manufacturing Practice.

[131] Okura and Matsuyama, Chap. 7, Sects. 7.2.4.2 and 7.3.2.5 (this volume).

Medicinal Products'. In the United States, FDA has released several, highly specific guidance notes relating to the manufacturing of cell/gene therapy products.[132]

9.4.4 GMO-Specific Requirements

Within the EU, GMO-related regulations come into play whenever the medicinal product is a GMO, consists of GMOs or contains GMOs. Since genome-edited iPSC-based cell/gene therapy products are made up of genetically engineered cells,[133] these products are GMOs within the meaning of EU law. Consequently, the application for marketing authorization must include certain documents and data packages which have their basis in the EU Directive 2001/18/EC on the deliberate release of GMOs into the environment. In a similar vein, albeit not being an EU Member State, also Switzerland requires applicants to furnish an environmental impact assessment (EIA) in accordance with the aforementioned EU Directive.[134] Arguably, the Swiss Gene Technology Act (GTA) might be applicable additionally.[135]

Although the United States has not enacted legislation specifically addressed to GMOs on the federal level, Biologic Licence Applications (BLAs) must be accompanied by an environmental assessment (EA).[136] This applies, in particular, to most gene therapy products unless they contain substances which occur naturally in the environment.[137] However, in case of cell-based gene therapy products, such as genome-edited iPSC-based cell/gene therapy products, FDA will not require an EA if the genetically modified cells cannot survive in the open environment and will be degraded to substances which also occur in nature.[138] In addition, genome-edited iPSC-based cell/gene therapy products will not be subject to the EA requirement if the genetic modification caused by genome editing techniques results in mutations which could occur during natural reproduction as well.[139]

[132] For an overview of applicable FDA guidance notes see Sanzo, Chap. 6, Sect. 6.2 (this volume).
[133] See *supra* Sect. 9.2.1.2.2.
[134] Dederer and Frenken (2021), pp. 36–37.
[135] Schweizer et al., Chap. 5, Sects. 5.2.1.1.3 and 5.3.3 (this volume).
[136] See *supra* Sect. 9.3.4.
[137] FDA (2015), pp. 5–6.
[138] FDA (2015), p. 7.
[139] FDA (2015), pp. 6–7.

9.5 Treatment Without Prior Marketing Authorization

There may be exceptional cases in which a medicinal product has not received marketing authorization yet but, nevertheless, should be made available to individual patients or a particular group of patients. This does, however, not imply that the medicinal product at issue may be administered without prior administrative oversight at all. Quite the contrary, in all countries under review, treatment of individual patients or particular patient groups using medicinal products, which have not been authorized for placing on the market, is subject to prior consent by the same public authority which is competent for the marketing authorization.

9.5.1 Single-Patient Treatments

In the EU, as regards ATMPs, two rules allow for single-patient treatment without prior marketing approval of the medicinal product administered to the patients. These rules are exemptions from the general requirement that medicinal product must not be placed on the market or administered to patients outside clinical trials without prior authorization by the relevant competent authority.

The first exemption is the so-called 'hospital exemption' which covers specifically, and only, ATMPs. Hence, somatic cell/gene therapy products based on genome-edited iPSCs may fall within the ambit of the 'hospital exemption'. According to EU law, this exemption applies to ATMPs 'prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient'.[140] The several requirements of this clause have been implemented differently in the EU Member States. This holds true, *e.g.*, for France and Germany. *E.g.*, in France, unlike in Germany, an ATMP is not prepared 'on a non-routine basis' if the product is made available to two or more patients at the same time.[141] Whereas in France the competent authority, *i.e.* the Agence nationale de sécurité du médicament ou des produits de santé (ANSM), has to take a decision within a time limit of 120 days,[142] the German Paul-Ehrlich-Institut's (PEI) decision may be rendered only within 5 months.[143]

The second exemption is the so-called 'special needs exemption' which is also available for, but not limited to, ATMPs. Pursuant to EU law, this exemption requires that the relevant medicinal product is 'supplied in response to a bona fide

[140] Article 28(2) ATMP Regulation (EC) No. 1394/2007 and Article 3(7) Human Medicines Code Directive 2001/83/EC respectively.

[141] Mahalatchimy, Chap. 4, Sect. 4.3.2.1 (this volume).

[142] Mahalatchimy, Chap. 4, Sect. 4.3.2.1 (this volume).

[143] Frenken and Lüttge, Chap. 3, Sect. 3.3.4.2 (this volume).

unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility'.[144] Again, EU Member States have made differing use of this clause. Whereas, *e.g.*, France has opted for the 'special needs exemption', Germany has not.[145] In France, contrary to the 'hospital exemption', the 'special needs exemption' may be applied to more than one patient at a time. However, these several patients must be designated individually by name.[146]

Other countries under review have introduced instruments similar to the aforementioned 'hospital exemption' and 'special needs exemption'. *E.g.*, in the United States, the so-called 'expanded access use' exemption plays a role more or less equivalent to the EU's 'hospital exemption' or 'special needs exemption' respectively.[147] In Japan, regenerative medicinal products such as somatic cell/gene therapy products based on genome-edited iPSCs may be used outside clinical trials in accordance with the RMS Act.[148] Under the RMS Act, the use of such *ex vivo* cell/gene therapy products is not limited to clinical research purposes but extends to curative purposes as well, *i.e.* to therapeutic treatments within the context of private medical practice covered by the Medical Practitioner Act/Medical Service Act.[149]

9.5.2 Treatments of Patient Groups

Another exception from the prior marketing authorization requirement which allows for the treatment of patients belonging to a particular patient group is the 'compassionate use exemption'. This exception is based on 'compassionate', *i.e.* humanitarian considerations.

Under EU law, the group must comprise patients 'with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactorily by an authorised medicinal product'.[150] The exemption's scope of application extends to ATMPs but is restricted to medicinal products which are either under investigation in a clinical trial or which are already the subject of a pending application for marketing approval.[151]

EU Member States may have laid down additional requirements for 'compassionate use'. *E.g.*, in Germany, the medicinal product must be provided free of

[144] Article 5(1) Human Medicines Code Directive 2001/83/EC.

[145] Frenken and Lüttge, Chap. 3, Sect. 3.3.4.3 (this volume).

[146] Mahalatchimy, Chap. 4, Sect. 4.3.2.2 (this volume).

[147] Dederer and Frenken (2021), pp. 90, 95.

[148] See *supra* Sect. 9.3.6.1.

[149] Okura and Matsuyama, Chap. 7, Sects. 7.2.5.1 and 7.2.5.2 (this volume). In addition, see Maeda et al. (2015), p. 152; Tobita et al. (2016), p. 80.

[150] Article 83(2)(1) Biotech Medicinal Products Regulation (EC) No. 726/2004.

[151] Article 83(1), (2)(2), Annex I(1a) Biotech Medicinal Products Regulation (EC) No. 726/2004.

charge. In addition, the particular compassionate use programme only needs to be notified to the Paul-Ehrlich-Institut (PEI).[152] By contrast, in France, 'compassionate use' depends on a prior authorization by the Agence national de sécurité du médicament ou des produits de santé (ANSM).[153]

Other countries under review allow for more or less equivalent exceptions. *E.g.*, in Switzerland, medicinal products undergoing clinical trials may be applied to patients who do not participate in these trials. Nevertheless, also with regard to these 'outsiders', the investigational medicinal product must be administered in accordance with the particular clinical trial protocol and only upon authorization by Swissmedic.[154] In the United States, 'compassionate use' of a medicinal product is facilitated through the instrument of 'expanded access use'. Such 'expanded access use' must not compromise clinical trials. Accordingly, it is restricted to patients who are not eligible for such trials.[155] Japan offers 'compassionate use' of genome-edited iPSC-based somatic cell/gene therapy products through the instruments laid down in the RMS Act.[156]

9.5.3 In-house Manufacturing and Administration

A peculiar issue within the EU is that the scope of application of EU medicinal products law is restricted to cases in which the product is, or is intended to be, placed on the market.[157] The term 'placing on the market' denotes activities (*e.g.*, storage, offering, distribution) aiming at the transfer of control over the product to a third party, *e.g.*, within the context of the sale or other forms of supply of the product.[158] Accordingly, EU medicinal products law (including, in particular, the law applicable to ATMPs and, thus, to somatic cell/gene therapy products based on genome-edited iPSCs) is inapplicable if the respective product is prepared by a physician within his or her own premises and applied to his or her patients in the very same premises. Such a scenario is entirely left to Member State regulation.

In Germany, *e.g.*, such in-house manufacturing and application of ATMPs by physicians was only subject to the manufacturing licence requirement until recently (leaving considerable doubts as to whether physicians were aware of this legal requirement under existing medicinal products law at all). Only in 2019, the

[152] Dederer and Frenken (2021), p. 50.

[153] Mahalatchimy, Chap. 4, Sect. 4.3.2.2 (this volume).

[154] Dederer and Frenken (2021), pp. 56–57.

[155] Dederer and Frenken (2021), pp. 57, 90–91.

[156] See *supra* Sects. 9.3.6.1 and 9.5.1.

[157] Article 2(1) Human Medicines Code Directive 2001/83/EC; Article 3(1) Biotech Medicinal Products Regulation (EC) No. 726/2004.

[158] *Cf.*, *e.g.*, Section 4(17) Medicinal Products Act (Germany) and corresponding annotations by Rehmann (2020), § 4 AMG, para. 19.

legislature amended the Medicinal Products Act in order to oblige physicians to notify the Paul-Ehrlich-Institut (PEI) of any personalized administration of ATMPs. However, this notification does not lead to an assessment of safety, quality and efficacy of the particular ATMP by the PEI.[159]

9.6 Patients' Biological Data

In case of a somatic cell/gene therapy based on genome-edited iPSCs, the genetically corrected cells to be transplanted, injected or infused into the patient must be devoid of any genetic or other abnormalities. For that purpose, at least full genome sequencing, however, as the case may be, also full transcriptome and proteome sequencing, may be necessary to ensure that the cells are both functional and safe. Such extensive sequencing inevitably discloses an enormous amount of personal biological data, *i.e.* genomic, transcriptomic and proteomic data, of the donor[160] or, in case of autologous therapies, of the patient. Such health-related data may, *e.g.*, reveal hitherto unknown dispositions for diseases, but, as the case may be, also other sensitive information related to the physical and mental health of the donor or patient respectively.

In the countries under review, personal data is, in general, protected. However, the degree of legal protection seems to differ remarkably. In some countries, *e.g.*, in Germany, Korea and Switzerland, the constitution enshrines basic rights protecting personal data, including health-related or biological data.[161] The same applies to the EU the fundamental rights charter of which lays down the right to respect for private life (Article 7 EUChFR) as well as the right to the protection of personal data (Article 8(1) EUChFR). The States which are bound by the ECHR, *i.e.* France, Germany and Switzerland, also have to comply with the convention's right to respect for private life (Article 8(1) ECHR) which, according to the jurisprudence of the ECtHR, includes personal data protection.[162] The aforementioned three States are also parties to the European Convention for the Protection of Data adopted within the framework of the Council of Europe (CoE).[163]

In addition, legislatures of all countries under review have enacted statutes which provide for personal data protection in general or for protection of health-related data in particular. As regards general data protection law, the EU Member States have to

[159] Dederer and Frenken (2021), pp. 51–52.

[160] Of those somatic cells which were reprogrammed into iPSCs.

[161] Frenken and Lüttge, Chap. 3, Sect. 3.4.1.1 (this volume); Shin, Chap. 8, Sect. 8.4 (this volume); Schweizer et al., Chap. 5, Sect. 5.5.1 (this volume).

[162] *Cf.* Mahalatchimy, Chap. 4, Sect. 4.4 (this volume); Schweizer et al., Chap. 5, Sect. 5.2.1.1 (this volume).

[163] Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data of 1981. As regards Switzerland see Schweizer et al., Chap. 5, Sect. 5.5.1 (this volume).

comply with the directly applicable General Data Protection Regulation (Regulation (EU) 2016/679—GDPR). Apparently, the GDPR has had a harmonizing effect throughout Europe provoking amendments to the CoE's Data Protection Convention and, thereby, influencing national data protection law of non-EU Member States such as Switzerland.[164]

The regulatory consequences arising from the common normative understanding that personal, including health-related and biological, data deserves to be protected are quite diverse. *E.g.*, it seems to be a unique feature of the French regulatory framework that the Commission nationale de l'informatique et des libertés (CNIL), *i.e.* a special data protection authority, is involved in the prior authorization procedures regarding clinical trials or treatments under the exemption[165] clauses. In such situations, according to French law, the processing of health data for purposes of research or ensuring safety and quality of the medicinal products administered to the patients is subject to prior authorization by CNIL.[166]

Another regulatory issue is whether and to what extent pseudonymized or anonymized data is protected. *E.g.*, in the United States, so-called de-identified data which is not linked any more to certain identifiers is not covered by the pertinent data protection law.[167] The use of not de-identified data for secondary research is permissible on the basis of consent by the patient concerned only.[168] This applies to biospecimens, too, unless they are sufficiently de-identified.[169] In contrast, in Switzerland, secondary research using de-identified genetic data or biological material requires prior informed consent of the patient concerned. Generally, broad consent is sufficient, though.[170] However, if the genetic data or the biological material is irreversibly anonymized, this informed consent requirement is reduced to a declaration by the patient that he or she does not object to the anonymization of the genetic data or biological material to be used for research purposes.[171] In Korea, personal data must be anonymized in case of data transfer even if the patient concerned has expressed his or her consent to such transfer. Of course, the anonymization requirement may be waived by the patient.[172]

[164] Schweizer et al., Chap. 5, Sect. 5.5.1 (this volume).

[165] 'Hospital exemption', 'special needs exemption' and 'compassionate use exemption'.

[166] Mahalatchimy, Chap. 4, Sect. 4.4 (this volume).

[167] Sanzo, Chap. 6, Sect. 6.3 (this volume).

[168] Sanzo, Chap. 6, Sect. 6.3 (this volume).

[169] Sanzo, Chap. 6, Sect. 6.3 (this volume).

[170] Schweizer et al., Chap. 5, Sect. 5.5.2.2 (this volume).

[171] Schweizer et al., Chap. 5, Sect. 5.5.2.2 (this volume).

[172] Shin, Chap. 8, Sect. 8.4 (this volume).

9.7 Germ Line Therapy

Germ line therapy may be carried out by genetically modifying germ cells or germ line cells. For the purpose of curing hereditary diseases, a preferable way to correct the particular genetic defect might be to genetically modify either the germ cells before *in vitro* fertilization or the embryo at its earliest possible developmental stage, *i.e.* at the pronuclear stage or at the zygote stage. A particularly safe way to generate genetically corrected germ cells might be to derive gametes artificially from genetically modified iPSCs.[173] Any genetic modification of egg or sperm cells used for *in vitro* fertilization or of pronuclear or single-cell-embryos would be passed on to future generations unless a special mechanism provided for a reversal of the genetic modification allowing for a 'one-generation germ line therapy'.[174]

For the time being, scientists consider germ line therapies entirely irresponsible, though, and, therefore, condemned human experiments which resulted in the birth of at least two twin babies in China in 2018, and called for a moratorium.[175]

Against this background, all countries reviewed adhere to strict prohibitions of germ line therapies either *de iure* or *de facto*. In Germany, germ line therapies are prohibited under the Embryo Protection Act which forms part of German criminal law. The reasoning underlying this absolute prohibition is that such therapies would require human experiments which were, for the time being, ethically unacceptable.[176] The same rationale prompted Korea to lay down a prohibition of germ line therapies in its Bioethics Act making any violation of the prohibition a criminal offense.[177] In contrast, France invoked the 'integrity of the human species' within the regulatory context of its prohibition of germ line therapy laid down in the Bioethics Code.[178] Switzerland, in turn, enshrined the prohibition of germ line therapies in its federal constitution. On the basis of its Reproductive Medicine Act, the perpetration of this prohibition constitutes a criminal offense.[179] Unlike Germany, both France and Switzerland are also bound by the CoE's Biomedicine Convention[180] which stipulates that any intervention into the human genome must not be allowed 'if its aim is . . . to introduce [a] modification in the genome of any descendants' (Article 13 Biomedicine Convention). According to both the EU's Clinical Trials Directive 2001/20/EC (Article 9(6)(2)) and the EU's new Clinical

[173] Cantz, Chap. 2, Sects. 2.3 and 2.4 (this volume).

[174] For a proposal of a concept for a 'one-generation germ line therapy' see Cantz, Chap. 2, Sect. 2.5.2 (this volume).

[175] See, *e.g.*, Lander et al. (2019).

[176] Frenken and Lüttge, Chap. 3, Sect. 3.6 (this volume); Dederer and Frenken (2021), p. 66.

[177] Shin, Chap. 8, Sect. 8.6 (this volume).

[178] Mahalatchimy, Chap. 4, Sect. 4.6 (this volume).

[179] Schweizer et al., Chap. 5, Sect. 5.4.2 (this volume).

[180] See *supra* Sect. 9.2.1.1.

Trials Regulation (EU) No. 536/2014 (Article 90(2)), '[n]o gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity'. Accordingly, Member States must not authorize clinical trials of germ line therapies. In Japan, clinical studies related to germ line therapies are prohibited as well, albeit on the basis of ministerial guidelines only.[181] Plans for a law prohibiting germ line therapies have not materialized so far.[182] The legal situation in the United States is peculiar in that, on the federal level, neither laws and regulations nor any guidance notes explicitly provide for a prohibition of germ line therapies.[183] Nevertheless, such a prohibition arises from budgetary constraints of FDA. According to the annual federal budget acts, the FDA is prevented from authorizing uses of investigational medicinal products which aim at germ line therapies.[184]

9.8 Conclusions

The conclusions to be drawn from the foregoing comparative analysis relate, first of all, to regulatory aspects. The relevant subsection (*infra* Sect. 9.8.1) is intended to identify best regulatory practices[185] as regards the regulation of somatic cell/gene therapies, in particular those which are based on genome-edited iPSCs, of germ line therapies and of biological data protection. However, effective translation of basic research into clinical applications does not only, or primarily, depend on the regulatory framework governing the respective activities. What has to be taken into account as well are other considerations, *e.g.*, financial or institutional aspects (*infra* Sect. 9.8.2).

9.8.1 Best Regulatory Practices

9.8.1.1 Three-Layered Regulatory Framework

As regards the overall structure of a regulatory framework applicable to genome-edited iPSC-based cell/gene therapies, a three-layered model seems to be proven and tested. Such a regulatory framework is made up of statutes passed by (parliamentary) legislatures on the first layer, regulations adopted by the executive, *e.g.*, by ministries or regulatory agencies, on the second layer, and guidelines issued, again, by the

[181] Ishii (2020), p. 457.

[182] Okura and Matsuyama, Chap. 7, Sect. 7.6 (this volume).

[183] Dederer and Frenken (2021), p. 66; *cf.* also Sanzo, Chap. 6, Sects. 6.1.1 and 6.5 (this volume).

[184] Charo (2020), pp. 454–455; Macintosh (2020), pp. 110–111.

[185] Regarding the criteria for the identification of best regulatory practices see *supra* Sect. 9.1.

executive, *e.g.*, by ministries, regulatory agencies or scientific agencies, on the third layer. Obviously, this three-layered framework constitutes a highly functional cascade of ever more technical and detailed norms.

9.8.1.2 Regenerative Medicine-Specific Regulations

The rules applicable to genome-edited iPSC-based cell/gene therapies form, in the first instance, part of well-established medicinal products law. Nevertheless, regulators have been aware of the fact that these highly innovative therapies belong to the evolving field of regenerative medicine. Regenerative medicinal products are, however, essentially different from small molecule drugs or biopharmaceuticals. Therefore, the regulation of regenerative medicinal products in general, and genome-edited iPSC-based cell/gene therapy products in particular, indispensably requires special norms adapted to the known and emerging specificities of this distinct category of medicinal products.

9.8.1.3 Centralized Bodies

It seems to be a tried system of governance that the rules applicable to genome-edited iPSC-based cell/gene therapies are executed by centralized bodies. This implies that, within federal systems of government, the competent authorities, *e.g.*, ministries, regulatory agencies or scientific agencies, are federal institutions. These centralized bodies are, as a rule, responsible not only for granting authorizations, or reviewing notifications, related to clinical investigations and marketing of medicinal products but also for issuing manufacturing licences. Accordingly, the German legislature might consider to confer also the power of administrative oversight of ATMP manufacturing upon the federal government, *i.e.* upon the Paul-Ehrlich-Institut (PEI).

In contrast, ethical review of clinical trials is carried out by committees or commissions established, typically, on the local or regional level. Nevertheless, the German legislature might consider to follow the example of Korea which set up a 'National Regenerative Medical Review Committee'. Centralizing ethical review on the national, or on the federal, level provides the advantage of consistent review standards for all clinical investigations wherever they are conducted within the State's territory and facilitates ethical reviews in case of multicentre clinical trials.

9.8.1.4 Avoiding Undue GMO Regulation

In the EU, GMO legislation has been clearly identified as overly burdensome ballast in the ongoing COVID-19 pandemic. Therefore, the EU legislature has, albeit only temporarily, facilitated the development of anti-SARS-CoV-2 vaccines and anti-

COVID-19 drugs by lifting certain requirements imposed by GMO legislation. Obviously, the Union legislature is of the opinion that human health clearly outbalances risks allegedly arising from genetic engineering. From our point of view, a similar reasoning should apply to genome-edited iPSC-based somatic cell/gene therapies. These therapies aim at the treatment of hereditary and most often severe and hitherto incurable diseases by correcting the relevant genetic defects, thereby eradicating the root causes of these diseases. In such a scenario, risks due to genome editing can be considered negligible or, at the very least, acceptable in light of substantial health benefits for patients suffering from serious and incurable hereditary diseases. Such a balancing of individual patients' interests versus general environmental and health concerns seems all the more adequate if, and to the extent that, genome editing causes point mutations only which could occur naturally as well.

9.8.1.5 Facilitated, or Differentiated, In Advance Control of Clinical Trials

The preferred in advance control mechanism for clinical trials seems to be the prior authorization instrument which means that clinical trials may proceed only after express consent by the relevant competent authority even if the time limit for review of the corresponding application has elapsed. However, the example of FDA (*i.e.* the competent regulatory agency of the United States) shows that the concept of prior notification, according to which sponsors or investigators may start their clinical trials after expiry of a waiting period of only 30 days unless FDA has put the trial on clinical hold, works perfectly as well. Admittedly, the extremely short timeline of 30 days sets FDA under high pressure. On the other hand, no doubt, FDA is one of the most, probably *the* most, experienced medicinal products agency in the world having accumulated outstanding expertise in drug regulation. Nevertheless, the competent bodies of other jurisdictions under review might have, basically, caught up with FDA. Legislators should, therefore, explore the idea to switch to the prior notification scheme combined with a waiting period of 30 days.[186]

A compromise between the prior authorization approach coupled with a 90 day review period (EU, France, Germany) and the prior notification approach coupled with a 30 day review period (Japan, United States) could be to adopt a tiered, risk-based approach. Japan and Korea provide examples of regulatory frameworks which make distinctions between three classes of risks (*i.e.* high, medium and low risks) of clinical research or clinical trials respectively.[187] Such a risk classification scheme could form the basis for a differentiated risk-based system of in advance control instruments. *E.g.*, prior notification coupled with a 30 day waiting period would be

[186] As regards France and Germany, such a regulatory change would require an amendment to pertinent EU legislation, of course.

[187] See *supra* Sect. 9.3.6.

reserved to low-risk trials whereas prior authorization coupled with a 60 or 90 day review period would be applicable to medium- and high-risk trials respectively. Of course, early consultation mechanisms would be essential in order to get academic researchers, sponsors and investigators onto the right regulatory track.

9.8.1.6 Early Consultation Mechanisms

Indeed, early consultation with the competent authorities is fundamental in case of somatic cell/gene therapy trials, especially as regards therapies which are based on genome-edited iPSCs. Such communication should start already well before pre-clinical studies, *i.e.* in the research phase when the possible translational pathway towards a potential clinical application becomes visible. In case of such highly innovative products as iPSCs and such highly innovative genetic modification techniques as genome editing, communication between researchers, investigators and sponsors on the one hand and regulators on the other hand should be close, intense, trustful and transparent. In fact, such consultations constitute a mutual learning process benefitting researchers, investigators and sponsors as well as regulators.

Another problem is that competent authorities may, or may have to, charge fees for providing consultation and advice services. It seems appropriate to distinguish, as regards the amount of such fees, between academic research institutions and hospitals on the one hand and pharmaceutical enterprises on the other hand. The latter may factor in the fees into the prize of the product when placed on the market. Accordingly, fees should be reduced or even not imposed in case of academic research institutions and hospitals.

9.8.1.7 Expedited Marketing Authorization Procedures

Somatic cell/gene therapies, especially *ex vivo* therapies based on genome-edited iPSCs, are designed, at least for the time being, to cure severe, often life threatening, and hitherto incurable diseases. At the same time, these therapies are highly innovative making use of completely novel therapeutic effects. Accordingly, academic researchers, sponsors and investigators developing such therapies deserve special support and attention by the competent authorities. In addition, as soon as it can be reasonably anticipated that, on the basis of research, pre-clinical and clinical data, such therapies seem to be sufficiently safe and effective, they should be made available to patients. Therefore, in line with the regulatory frameworks of the jurisdictions under review, special marketing authorization procedures should be established which allow for continuous and close interaction between (potential) applicants and competent authority as well as for expedited and, as the case may be, 'rolling' review on the basis of provisional data within shorter time lines. As a counter-balance, marketing authorizations resulting from such special procedures

have to be time-limited (albeit renewable) and conditional (*e.g.*, granted upon the condition that further clinical trials are carried out).

9.8.1.8 Permissibility of Treatment Prior to Marketing Authorization

It is well-established that there are exceptional cases of patients who are in desperate need of therapeutic treatment by means of novel, highly innovative medicinal products which have not received a marketing authorization yet. This will certainly hold true for future genome-edited iPSC-based somatic cell/gene therapy products as well. The reason for the lack of a marketing authorization may be that clinical trials are still ongoing and the currently existing research, pre-clinical and clinical data does still not even warrant a provisional authorization. If individual patients or particular patient groups are ineligible for these clinical trials, they cannot even benefit from treatment in the course of clinical investigations already taking place. Another reason might be that, at least for the foreseeable future, it may not be possible to generate sufficient reliable data through clinical trials with the particular medicinal product at all. In all these situations, individual patients or particular patient groups should not be strung along (until a marketing authorization will be issued, if at all) but, rather, should get treatment for humanitarian reasons, *e.g.*, if they suffer from a life-threatening or otherwise extremely severe disease. On the other hand, the preferred way to make medicinal products, including iPSC-based cell/gene therapy products, widely available to patients should be, in general, that the relevant products undergo thorough and state-of-the-art clinical investigations. Hence, regulatory frameworks should enable, and even facilitate, treatment with highly innovative medicinal products prior to, or without, marketing authorization albeit under restrictive conditions only.

9.8.1.9 Abolishing the Additional Manufacturing Licence Requirement

Admittedly, it seems to be a well-established regulatory standard to require that (investigational) medicinal products may be produced on the basis of a separate manufacturing licence only. However, it is, again, the United States which provides the example of a more flexible regulatory framework that does not know an additional manufacturing licence requirement. Instead, sponsors, investigators or pharmaceutical enterprises have to submit so-called 'CMC' ('Chemistry, Manufacturing, and Control') information convincingly demonstrating the safety, identity, quality, purity, and strength[188] of the somatic cell/gene therapy product.

In any case, manufacturing should conform to GMP standards, in general. However, competent authorities should accord sufficient flexibility to sponsors and investigators, especially in the early phases of clinical trials. It is in the very nature of

[188] *Cf.* 21 CFR 312.23(a)(7)(i).

ex vivo somatic cell/gene therapy products that they are under continuous development as long as they are at the research and development stage. Accordingly, requiring unconditional compliance with full GMP standards may unduly impede, or even rule out, product development, in particular by academic researchers, hospitals and small biotech enterprises.[189]

9.8.1.10 Differentiated Prior Informed Consent Requirements

The use of biological data, *e.g.*, genomic, transcriptomic or proteomic data, of the donor[190] or of the patient[191] is inevitable in the course of clinical trials with genome-edited iPSC-based somatic cell/gene therapy products.[192] The same holds true, *e.g.*, for treatments of individual patients with corresponding products which have not, or not yet, been authorized for placing on the market.[193] This use of an extremely broad spectrum of biological data, implying full genome and, as the case may be, transcriptome and proteome sequencing as well as in-depth data analyses by means of big data and high throughput technologies, raises the legal issue of personal data protection.

In line with the principle of personal data autonomy, the use, including the generation, storage, processing, analysis and transfer, of biological data must be authorized by the donor or patient respectively. The means of such authorization is informed consent. However, personal data autonomy has to be balanced against other concerns involved, *e.g.*, freedom of research for the purpose of the development of therapies for severe and hitherto incurable hereditary diseases. Accordingly,[194] the informed consent requirement should be tiered in accordance with the will of the donor or patient as well as the kind of data and its use. This tiered system of informed consent might be framed as follows.

Any use of any biological data is unlawful if it is contrary to the original consent of the donor or patient. Hence, the donor's or patient's original consent may include certain express prohibitions regarding certain uses of certain biological data no matter whether the data is de-identified or not. In the absence of such express prohibitions, the legality of the use of biological data should be dependent on whether the data is de-identified or not. If the biological data is not de-identified (*i.e.* neither pseudonymized nor anonymized) specific informed consent by the patient or the donor to any use should be the rule. The informed consent is specific

[189] Dederer and Frenken (2021), pp. 80, 93–94, 100, 102.

[190] In case of allogenic therapies, *i.e.* if the iPSCs have been derived from somatic cells of a person other than the patient.

[191] In case of autologous therapies, *i.e.* if the iPSCs have been derived from somatic cells of the patient.

[192] *Cf. supra* Sect. 9.6.

[193] For such treatments see *supra* Sect. 9.5.

[194] Taking, to a certain extent, Switzerland's and the United States' data protection regulations as models. See *supra* Sect. 9.6; Schweizer et al., Chap. 5, Sect. 5.5.2.2 (this volume); Sanzo, Chap. 6, Sect. 6.3 (this volume).

if it is related to precisely specified uses for precisely specified purposes. However, if the biological data is pseudonymized, broad consent by the patient or the donor should be considered sufficient. Broad consent means that the consent is related to sufficiently specified uses for sufficiently specified purposes. If the biological data is anonymized, the informed consent requirement should be reduced to a declaration of the donor or patient that he or she does not object to any use for any purpose if, and to the extent that, the biological data is definitely anonymized.

9.8.1.11 Moratorium on Germ Line Therapies

It is the unanimous view of the global scientific community that germ line therapies must be prohibited for the time being as far as genetic modifications of the germ line are heritable, *i.e.* passed on to future generations.[195] Due to the current state of science and technology, even clinical trials or clinical studies or any other research involving human beings have to be considered ethically totally unacceptable. However, assuming that, due to future scientific and technological developments, the risks resulting from genetic modification of the germ line using genome editing techniques might be not higher than the risks arising from natural mutations occurring, *e.g.*, during regular cell division or caused by ionising radiation from natural sources, the benefits will very probably outpace the risks and call for a permission of germ line therapies. Nevertheless, even in such scenarios involving a generally acceptable risk-benefit ratio there may be unpredictable long-term risks emerging only after decades or becoming visible only in the next or the next but one generation. Therefore, germ line therapies, albeit if considered sufficiently safe for the individuals resulting from, *e.g.*, genetically corrected embryos, should be permitted only under strict formal and substantive requirements.[196]

9.8.2 Additional Considerations

The comparative analysis of the regulatory frameworks of the jurisdictions under review formed the basis for the tentative identification of best regulatory practices (*supra* Sect. 9.8.1). However, successful translation of basic research into clinical applications depends not only on the applicable regulatory environment but also on other factors as well. As these other factors are, basically, beyond the focus of the country reports and, hence, of this comparative analysis, they will be outlined hereinafter only very briefly.

[195] National Academy of Sciences (2020).

[196] For an overview of possible requirements for permissible germ line therapies see, *e.g.*, Schleidgen et al. (2020), pp. 9–11.

Clinical trials require enormous financial means,[197] especially when clinical trials proceed towards phase III. Phase III-trials need a financial basis in the upper double-digit millions. Public funds are, typically, limited and will in most cases not suffice to cover the expenses of phase III-clinical trials. It is, therefore, indispensable that private venture capital is available. However, satisfactory availability of private risk capital seems to be not only a matter of a country's wealth but also of a country's rather entrepreneurial than risk-averse culture. In order to improve the venture capital climate within their country, governments may have to reflect means and methods to incentivize the raising and supply of private risk capital.

Whether a somatic cell/gene therapy product will be an economic success does not only depend on how streamlined the regulatory process is. Typically, at least for the time being, somatic cell/gene therapy products are extremely expensive.[198] Of course, the costs for a somatic cell/gene therapy, which wipes out the root causes of a hereditary disease by just one single treatment, have to be counterbalanced against the costs of a conventional therapy, which only cures or tempers the symptoms of the same disease necessitating continuous and even, as the case may be, life-long treatment with likewise expensive medicinal products. Nevertheless, currently, private and social health insurers seem to be hesitant as regards coverage of expenses related to somatic cell/gene therapies. However, somatic cell/gene therapy products will disappear from, or not even enter, the market if their costs are not reimbursed because the individual patients themselves will, usually, not be in a position to pay the expenses. Accordingly, it is almost indispensable that the research and development process of a somatic cell/gene therapy product and the design of a reimbursement scheme are dovetailed.[199] It is equally important to align the research and development process with analyses regarding the scaling up of product manufacturing processes and competing treatments readily available on, or expected to enter, the market.[200]

Clinical trials with somatic cell/gene therapy products, especially if based on genome-edited iPSCs, are extremely complex. This complexity relates, on the one hand, to the specific biological nature of these products requiring special manufacturing, storage and transport conditions[201] and, on the other hand, to regulatory matters. For that reason, in particular academic researchers, hospitals and small biotech companies encounter a broad panoply of significant difficulties. Therefore, it seems advisable to provide them with infrastructural, technical and

[197] *Cf.* also Papenfuss (2020), p. 1668.

[198] *E.g.*, in Germany, the gene therapy medicinal product Zolgensma® is provided at a price of two million Euros. See Pitz (2020).

[199] *Cf.* Ginty (2020), pp. 1176–1177; *cf.* also, as regards Japan, Okura and Matsuyama, Chap. 7, Sect. 7.2.5.3 (this volume).

[200] *Cf.* Papenfuss (2020), pp. 1666, 1268.

[201] *Cf.* Ginty (2020), p. 1175.

regulatory expert support[202] facilitating the conduct of clinical research and clinical trials.

Finally, the number of somatic cell/gene therapy products in the research and development pipeline is steadily and significantly increasing. Accordingly, competent authorities are threatened to get overwhelmed by authorization applications or notifications respectively. Therefore, governments should seek to hire more staff endowed with the required special regulatory, scientific and technological expertise to review applications for authorization, or notifications, of somatic cell/gene therapy products to be used in clinical trials or placed on the market.[203]

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[202] *Cf.*, *e.g.*, in the United Kingdom (UK), the 'Cell and Gene Therapy Catapult'; regarding the UK's Advanced Therapy Treatment Centre (ATTC) network programme connecting three Advanced Therapy Treatment Centres coordinated by the Cell and Gene Therapy Catapult see Hollingsworth (2020).

[203] In that regard, it is of note that, in the United States, FDA planned to recruit 50 additional reviewers to be employed with the Office of Tissues and Advanced Therapies (OTAT) which is a special division of the Center for Biologics Evaluation and Research (CBER) within FDA. See Sanzo, Chap. 6, Sect. 6.2 (this volume).

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Appendix: Questionnaire

Country Report: [please state your country]

Introduction

The introduction should make the reader aware of the country's significance for (research on) gene therapies and cell therapies including stem cell-based therapies.

Facts that could be mentioned

• Clinical trials of somatic gene therapy products • Market authorizations for somatic gene therapy products • Genome editing, especially through CRISPR-Cas, in human cells/human iPS cells	• Research on cell therapies based on stem cells and iPS cells in particular • Research on gene therapies using genome editing techniques, e.g. CRISPR-Cas	• Clinical trials of, or experimental treatment using, cell therapy products derived from stem cells or, in particular, iPS cells • Clinical trials of, or experimental treatment using, combined cell/gene therapy products derived from genome edited stem cells, especially iPS cells

Genome Editing of Human iPS Cells: An Overview of the Regulatory Framework

Please give an overview of the regulatory framework concerning gene therapy and cell therapy. What are the applicable laws and regulations? Which public authorities are responsible for the administration of the regulatory regime? In case there is more than one competent authority: what are their responsibilities and what is the relationship between the different authorities?

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H.-G. Dederer, G. Frenken (eds.), *Regulation of Genome Editing in Human iPS Cells*, https://doi.org/10.1007/978-3-030-93023-3

Regulatory Prerequisites for Combined Gene/Cell Therapy Using Genome Edited Human iPS Cells to be Differentiated into Somatic Cells for Autologous Retransplantation

Please describe the administrative procedures, or administrative oversight mechanisms, for each step of such combined gene/cell therapies in detail. A subdivision into the following different steps might be useful: (1) biopsy of somatic, e.g. skin, cells, (2) reprogramming into induced pluripotent stem cells (iPS cells), (3) genome editing of iPS cells via, e.g., CRISPR-Cas, (4) redifferentiation into somatic cells (or progenitor cells) and (5) retransplantation into the patient.

Concerning the regulation of experimental treatment, clinical trials and placing on the market of combined cell/gene therapy products derived from genome edited iPS cells, we are especially interested in whether authorization or notification obligations apply, which requirements or standards must be met and how compliance is controlled: Is it (always or under which circumstances) necessary to submit an application for authorization or a notification? What are the (e.g. data, information, risk assessment) requirements for an application for authorization or for a notification? Under which circumstances will an authorization be granted?

Are the cells, whether the biopsied cells, the iPS cells, the genome edited iPS cells, the iPS cell-derived, and genetically modified, cells or cell transplants, classified as belonging to a special category of medical products, like, e.g., in the EU as 'Advanced Therapy Medicinal Products' (ATMP)?

When explaining the administrative procedures, or administrative oversight mechanisms respectively, please distinguish, if appropriate, the following scenarios (the background to these distinctions being that special permits might be required if cells or transplants are passed on from one entity to another, separate, entity):

1. The treating doctor only removes the somatic cells and transplants, or injects, the genome edited iPS cell-derived cells, while reprogramming, genome editing and redifferentiation take place in a specialised laboratory operated by a pharmaceutical manufacturer.
2. The entire process takes place in the treating doctor's surgery under the doctor's direction, technical supervision and responsibility.
3. The entire process takes place in one hospital but in separate departments, i.e. the biopsy of the patient's somatic cells, their reprogramming into iPS cells, the genome editing of the iPS cells and their redifferentiation as well as the transplantation, or injection, of the resulting cells are carried out in two or more different departments headed by different doctors or researchers respectively.

Treatment of the Patient's Biological Data

Based on the results of the previous section, please describe how the patients' biological (e.g. genomic, transcriptomic, metabolomic) data is to be handled if it

has to be submitted to public authorities or regulatory agencies in order to demonstrate, e.g., safety and quality of the genome edited iPS cell-derived cells or cell transplants.

Please explain whether, and, if so, to what extent, the patient's biological data is protected by a fundamental, or basic or constitutional, right (e.g., a right to (bio)-informational self-determination) or any other paramount legal principle. Where appropriate, please explain how this right or principle is denominated, what its status is in the hierarchy of norms or where it is, or can be, derived from. How does this right or principle relate to statutory law?

Please state to what extent and for what purposes biological (e.g. genomic, transcriptomic, metabolomic) data is to be transmitted to public authorities. How are these data to be treated (i.e. stored, protected, processed, passed on, e.g. to other entities for other purposes)?

Please explain, if applicable, whether and, if so, to what extent general data protection law is applicable.

Reform Efforts

How suitable is the current regulatory regime for gene therapy in human iPS cells to be differentiated into somatic cells for autologous retransplantation? Which shortcomings of the regulatory regime have to be mentioned with regard to such novel combined gene/cell therapies? Which strengths do you see?

Are there governmental plans (e.g. of the legislature or the executive) to update the current legal regime? Which proposals have been made? How would you assess these?

Do you have own recommendations for updating the current regulatory framework for gene therapy in human iPS cells to be differentiated into somatic cells for autologous retransplantation?

Outlook: Human Germ Line Intervention Through Genome Editing

Another way of treating certain serious, in particular hitherto incurable genetic, i.e. hereditary, diseases is to directly intervene into the germ line. Hence, by way of an excursus, please explain how interventions into the human germ line via, e.g., CRISPR-Cas are regulated:

Is germ line intervention through genome editing in human beings, especially genome editing in human single-cell embryos in the pronuclear or zygotic stage for the purpose of treating hereditary diseases legally prohibited or permitted (and, if so, under which conditions)? In case of a prohibition: Why did the legislator decide so?

If there are several reasons, please indicate which argument might have been decisive.

Reasons that could have led to a prohibition	
• Life and health risks for the genetically modified (born) human being • Life and health risks for future generations • Life and health risks for the pregnant woman	• Integrity of the human genome, or human germ line, as such • The State's fear of losing control over the use of CRISPR-Cas technology in humans (further development towards enhancement, 'designer babies', 'breeding programmes' etc.)

Conclusion

In the conclusion, please take stock of your findings.